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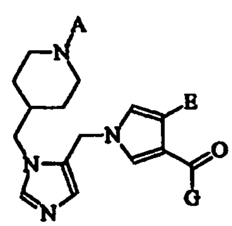

(1)

(57) Abstract

The present invention relates to a novel piperidine derivative represented by formula (1) which shows an inhibitory activity against farnesyl transferase or pharmaceutically acceptable salts thereof, in which A, E and G are defined in the specification; to a process for preparation of the compound of formula (1); to an intermediate which is used in the preparation of the compound of formula (1); and to a pharmaceutical composition comprising the compound of formula (1) as an active ingredient.

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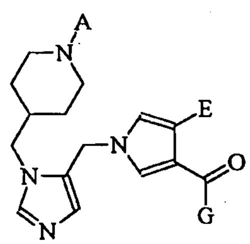
FARNESYL TRANSFERASE INHIBITORS HAVING A PIPERIDINE STRUCTURE AND PROCESS FOR PREPARATION THEREOF

TECHNICAL FIELD

The present invention relates to a novel piperidine derivative represented by the following formula (1) which shows an inhibitory activity against farnesyl transferase:



(1)

in which A, E and G are defined as described below, or pharmaceutically acceptable salts thereof.

The present invention also relates to a process for preparation of the compound of formula (1), to intermediates which are used in the preparation of the compound of formula (1), and to a pharmaceutical composition comprising the compound of formula (1) as an active ingredient.

BACKGROUND ART

Mammalian Ras proteins act as molecular switches in the signalling events associated with cell growth and differentiation. The ras proto-oncogene family consists of three members, N-, K-, and H-ras, which code for highly homologous 4 types of proteins; i.e., H, N-ras proteins of 189 residues and two isomorphic K-ras-4B and K-ras-4A

proteins of 188 and 189 residues, respectively. The chemical basis for the switch mechanism involves cycling of the protein between the inactive (off) guanosine diphosphate (GDP) bound state and the active (on) guanosine triphosphate (GTP) bound state (Bourne, H. R.; Sanders, D. A.; McCormick. F.; Nature, 1991, 349, 117). Biochemical and structural studies have shown that point mutations of the residues 12, 13 and 61, positioned in the neighborhood of phosphoryl ground of GTP, resulting in the decrease of guanosine triphosphatase activity are associated with many human cancers, particularly, pancreatic cancer, urinary bladder carcinoma, colon cancer, etc. (Bos, J. L., Cancer Res., 1989, 49, 4682).

Ras protein is synthesized as a cytosolic precursor that ultimately localized to the cytoplasmic face of the plasma membrane after a series of posttranslational modification (Gibbs, J. B., Cell 1991, 65, 1). These series of biochemical modifications, by changing the electrical charge state or spacial structure to increase the hydrophobicity allow Ras protein to attach to cell membrane more easily. The first and obligatory step in the series is the addition of a farnesyl moiety to the cysteine residue of the C-terminal CAAX motif (C, cysteine; A, usually aliphatic residue; X, any other amino acid) in a reaction catalyzed by farnesyl protein transferase (FTase). This modification is essential for Ras function, as demonstrated by the inability of Ras mutants lacking the C-terminal cysteine to be farnesylated, to localize to the plasma, and to transform mammalian cells in culture (Hancock, J. F., Magee, A. I., Childs, J. E., Marshall, C. J., Cell 1989, 57, 1167). The subsequent posttranslational modifications, cleavage of the AAX residues, carboxyl methylation of the the farnesylated cysteine, and palmitoylation of the cysteines located upstream of the CAAX motif in H- and N-ras proteins are not obligatory for Ras membrane association or cellular transforming activity.

Interestingly, K-ras-4B, different from H- and N-ras, has a multiple lysine rich region named polybasic domain, instead of having cysteine required for palmitoylation, thereby facilitating the farnesylated ras protein to bind to anionic lipid layer of cell membrane. The inhibitors of FTase that catalyzes the obligatory modification have therefore been suggested as anticancer agents for tumors in which Ras oncogene contributes to transformation (Buses, J. E. et al., Chemistry & Biology, 1995, 2, 787). A number of FTase inhibitors recently identified demonstrated potent and specific ability to block Ras farnesylation, signalling and transformation in transformed cells and tumor cell lines both in vitro and in animal models (Kohl. N. E. et. al., Proc. Natl. Acad. Sci. USA. 1994, 91, 9141; Kohl, N. E. et al., Nature Medicine, 1995, 1 792).

However, most of the inhibitors are related to CAAX motif as Ras substrate mimic and peptidic in nature or contain a sulfhydryl group (USP No. 5,141,851; Kohl, N. E. et. al., Science, 1993, 260, 1934; PCT/US95/12224, Graham et al.; Sebti, S. M. et. al., J. Biol. Chem., 1995. 270, 26802; James, G. L. et al., Science, 1993, 260, 1937; Bishop, W. R. et al., J. Biol. Chem., 1995, 270, 30611). Recently, a new type of peptidomimetic inhibitor imitating catalytic step of FTase has been reported (Poulter, C.D. et al., J. Am. Chem. Soc., 1996, 118, 8761). The chemical basis of the inhibitor design relates to the reaction mechanism. This is, transferring prenyl group by the enzyme is electrophilic displacement and the reaction requires (+) charge in a transition state.

These inhibitors previously described however possess limited activity and selectivity for inhibition of the oncogenic function of Ras proteins, particularly K-ras-4B, which is found to be most common in human cancer. Therefore, new inhibitor having the ability of effectively

inhibiting K-ras activity is required.

With regard to the restenosis and vascular proliferative diseases, it has been shown that inhibition of cellular ras prevents smooth muscle proliferation after vascular injury in vivo (Indolfi C. et al., Nature Med., 1995, 1(6), 541-545). This report definitively supports a role for farnesyl transferase inhibitors in this disease, showing inhibition of accumulation and proliferation of vascular smooth muscle.

DISCLOSURE OF INVENTION

The present inventors have performed studies for developing a compound having the structure characteristics imitating an intermediate state of catalytic reaction of FTase and as a result, found that piperidine derivatives according to the present invention can potently inhibit the enzyme.

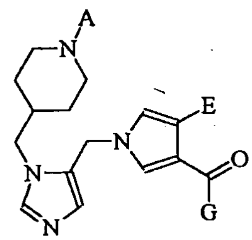
Therefore, the object of the present invention is to provide a piperidine derivative of formula (1) which inhibits the activity of FTase, process for preparation thereof, and a novel intermediate which can be used effectively in the process for preparing the compound of formula (1).

It is another object of the present invention to provide a pharmaceutical composition comprising the compound of formula (1) as an active ingredient.

BEST MODE FOR CARRYING OUT THE INVENTION

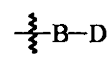
It is the first object of the present invention to provide a

piperidine derivative represented by the following formula (1) and pharmaceutically acceptable salts thereof which inhibit the activity of farnesyl transferase :



(1)

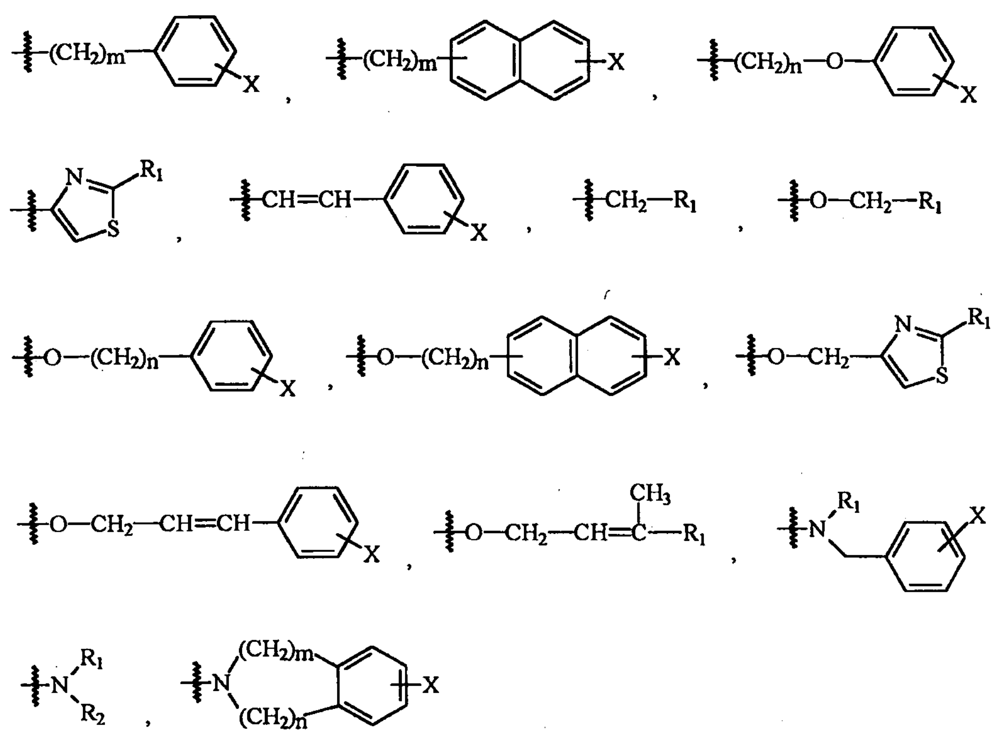
in which

A represents hydrogen, lower alkyl, or  ,

wherein

B represents CH_2, C=O or SO_2, and

D represents a radical selected from the following group:



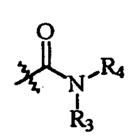
In the definition for the substituent D,

m denotes an integer of 0 to 3,

n denotes an integer of 1 to 3,

X represents hydrogen, phenyl, phenoxy, lower alkyl, lower alkoxy, halogen, nitro, or amino which is optionally substituted by benzyl or lower alkyl,

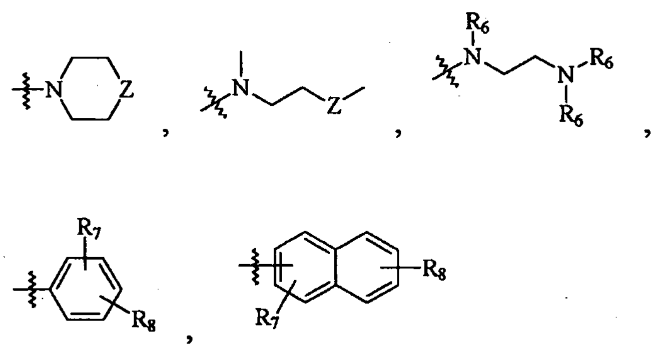
R_1 and R_2 independently of one another represent hydrogen, lower alkyl, C_3-C_6-cycloalkyl, lower alkyl substituted by C_3-C_6-cycloalkyl, aryl or heteroaryl,

E represents hydrogen, phenyl, naphthyl or  ,

wherein

R_3 and R_4 independently of one another represent hydrogen, lower alkyl, aryl or $-(CH_2)_{n'}-Y-R_5$ (wherein Y represents O or S, n' denotes an integer of 2 to 4, and R_5 represents lower alkyl),

G represents a radical selected from the following group:



wherein

Z represents O, S, SO_2 or N-R_6 (wherein R_6 represents hydrogen or lower alkyl),

R_7 and R_8 independently of one another represent hydrogen, lower alkyl, lower alkoxy, halogen, cyano, hydroxycarbonyl, aminocarbonyl, aminothiocarbonyl, hydroxy, phenyl or phenoxy.

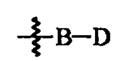
Particularly, the compound according to the present invention has a quite different structure from the known inhibitors for farnesyl transferase, and furthermore it does never include the thiol moiety.

In the definitions for the substituents of the compound of formula (1), the term "lower alkyl" means a straight-chain or branched alkyl having 1 to 4 carbon atoms which includes methyl, ethyl, isopropyl, isobutyl and t-butyl; the term "cycloalkyl" means cyclic alkyl which includes cyclohexyl; the term "aryl" means 6 to 14-membered

monocyclic-, bicyclic- or tricyclic aromatic group; and the term "heteroaryl" means 6 to 14-membered monocyclic-, bicyclic- or tricyclic aromatic group containing hetero atom(s) selected from a group consisting of oxygen, nitrogen and sulfur.

Also, the compound of formula (1) according to the present invention can form a pharmaceutically acceptable salt. Such salt includes non-toxic acid addition salt containing pharmaceutically acceptable anion, for example a salt with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydriodic acid, etc., a salt with organic carboxylic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trofluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid, asparagic acid, etc., or a salt with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, etc.; base addition salt for example a salt with pyridine or ammonia; and metal addition salt for example a salt with alkali metal or alkaline earth metal such as lithium salt. Further, the present invention includes a solvate of the compound of formula (1) such as alcoholate or hydrate thereof. They can be produced by conventional conversion methods.

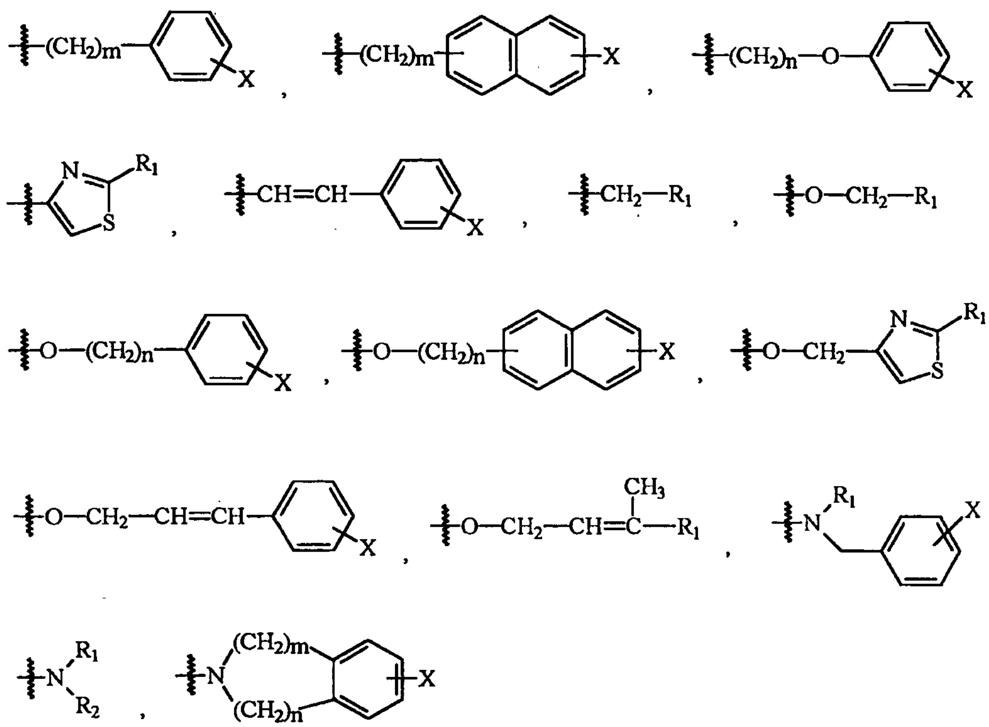
Among the compound of formula (1) according to the present invention, the preferred compounds include those wherein

A represents hydrogen, lower alkyl, or  ,

wherein

B represents CH_2, C=O or SO_2,

D represents a radical selected from the following group:



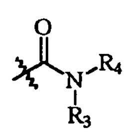
In the definition for the substituent D,

m denotes an integer of 0 to 1,

n denotes an integer of 1 to 2,

X represents hydrogen,

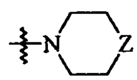
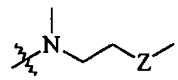
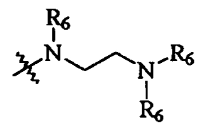
R_1 and R_2 independently of one another represent hydrogen or lower alkyl,

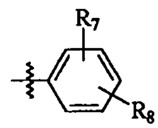
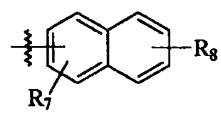
E represents hydrogen, phenyl, naphthyl, or  ,

wherein

R_3 and R_4 independently of one another represent hydrogen, lower alkyl, or 2-methoxyethyl,

G represents a radical selected from the following group:

 ,  ,  ,

 , 

wherein

Z represents O or N-R_6 (wherein R_6 represents methyl),

R_7 and R_8 independently of one another represent hydrogen.

Typical examples of the compound of formula (1) according to the present invention are presented in the following Table 1.

Table 1-1

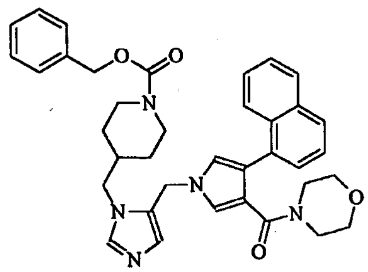
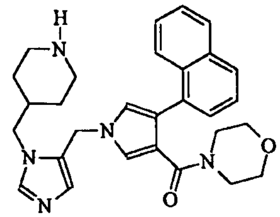
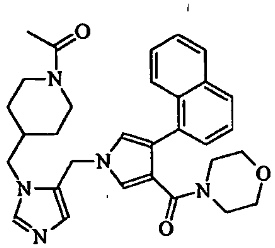
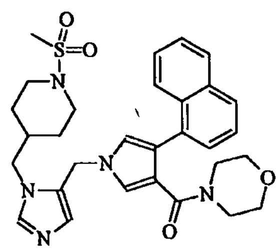
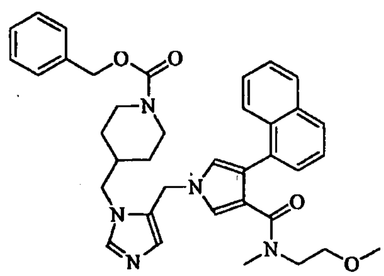
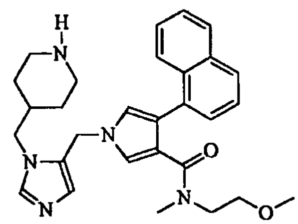
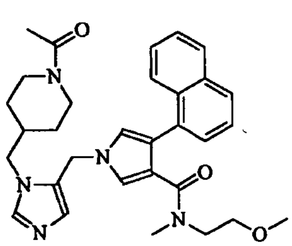
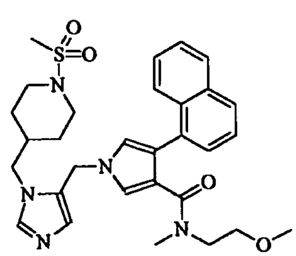
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
1		2	
3		4	
5		6	
7		8	

Table 1-2

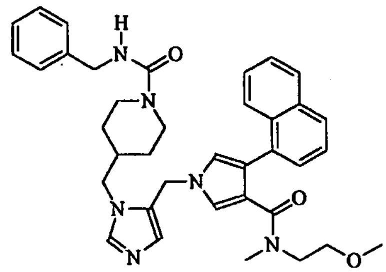
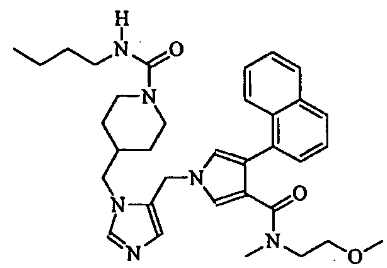
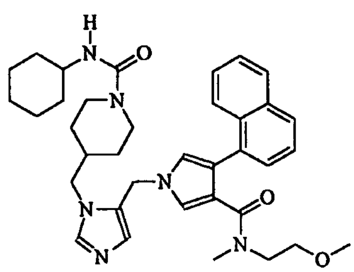
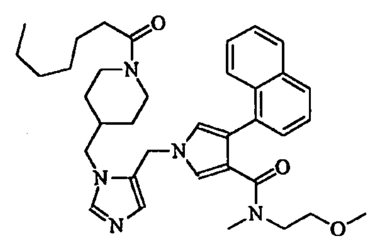
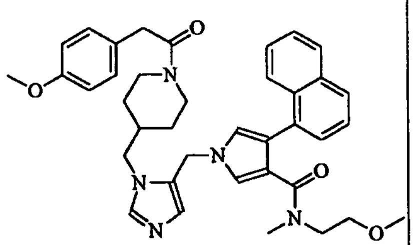
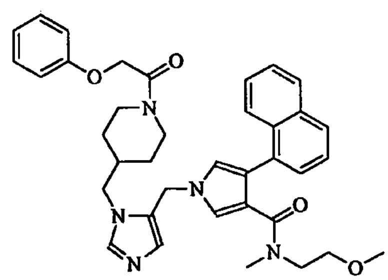
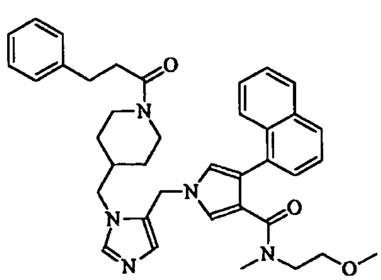
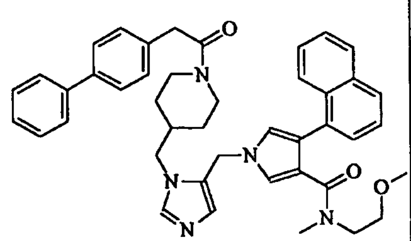
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
9		10	
11		12	
13		14	
15		16	

Table 1-3

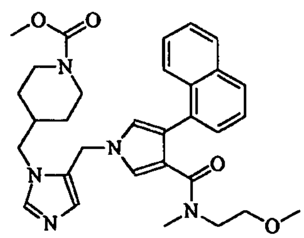
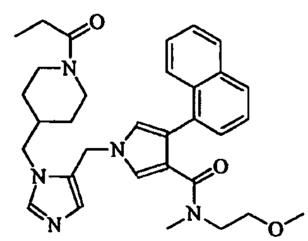
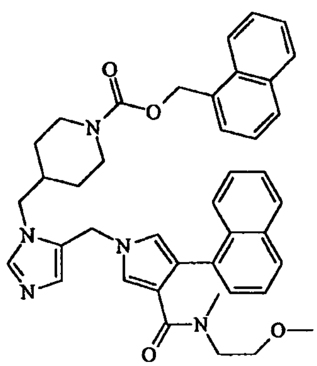
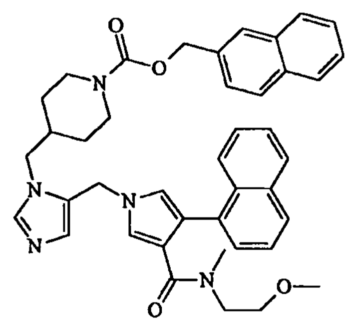
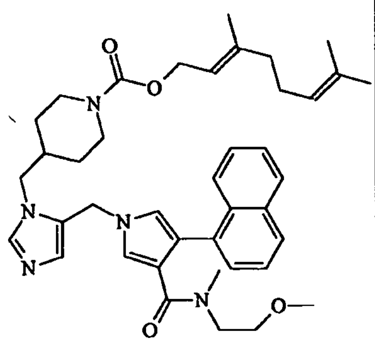
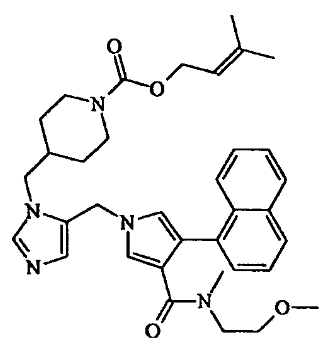
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
17		18	
19		20	
21		22	

Table 1-4

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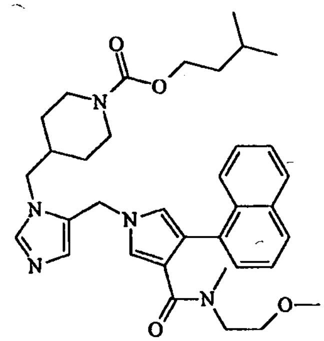
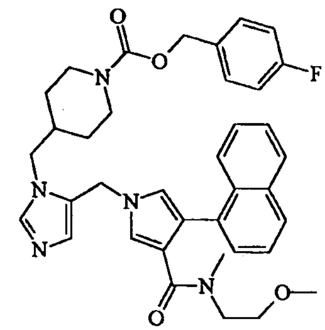
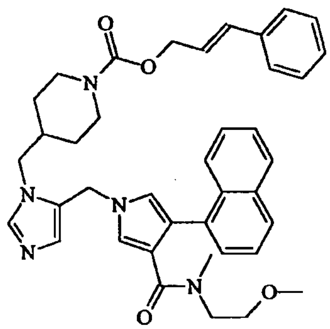
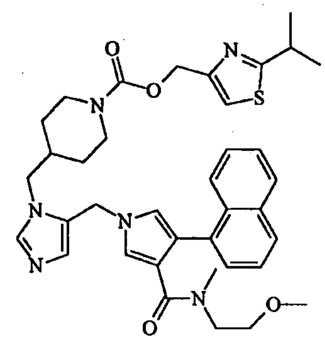
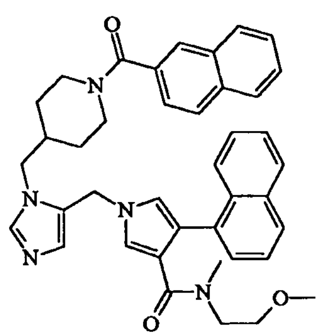
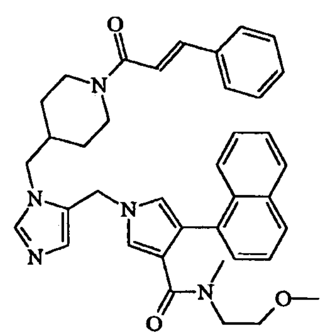
23		24	
25		26	
27		28	

Table 1-5

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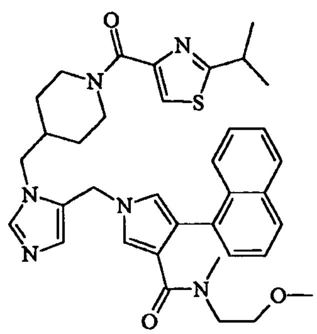
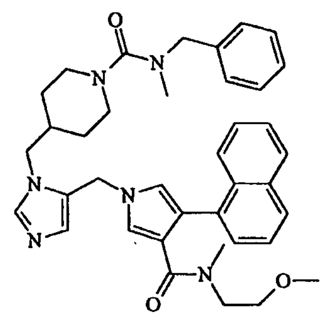
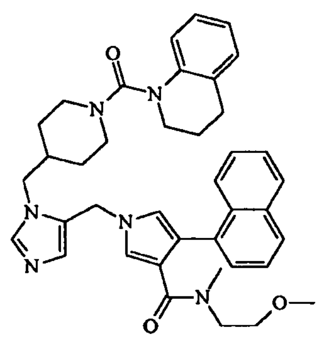
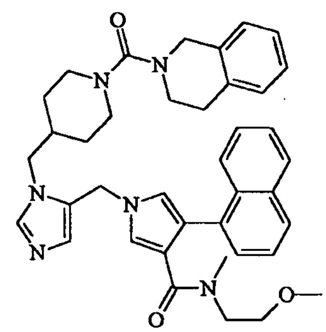
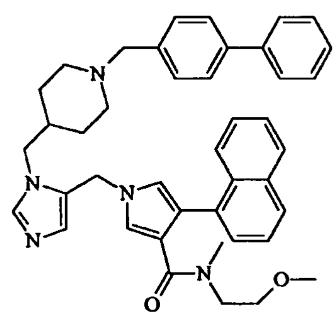
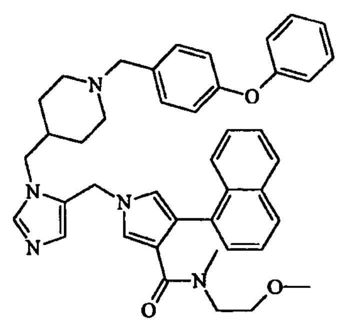
29		30	
31		32	
33		34	

Table 1-6

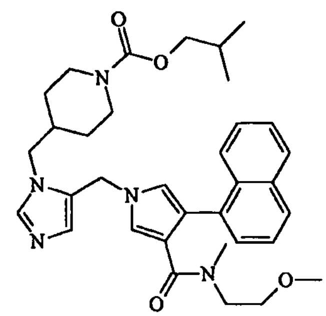
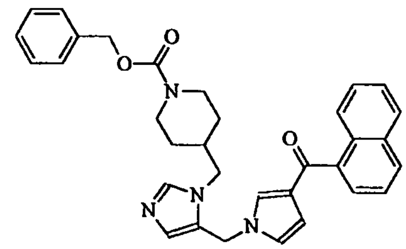
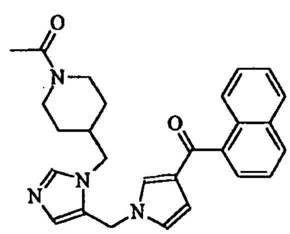
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
35		36	
37			

Table 1-7

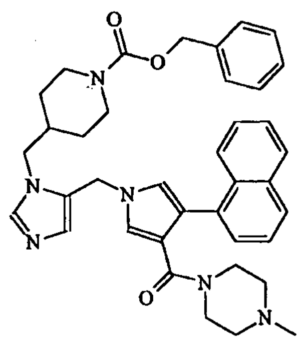
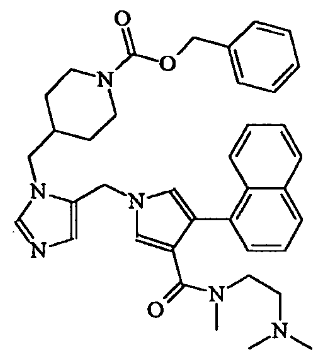
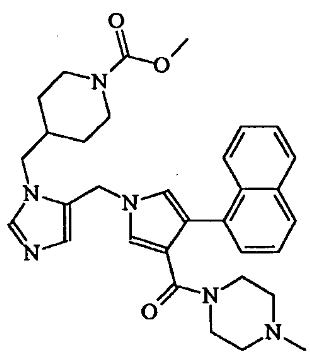
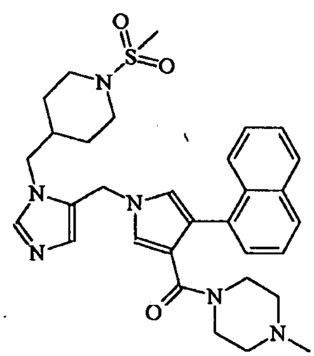
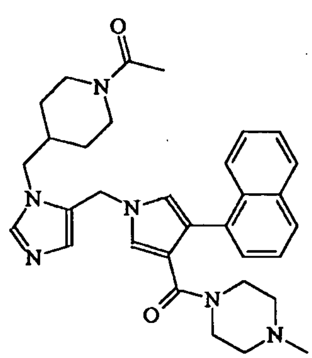
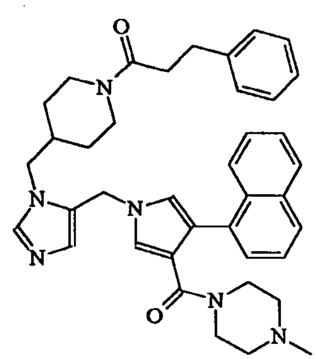
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
38		39	
40		41	
42		43	

Table 1-8

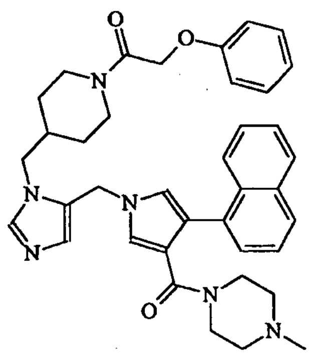
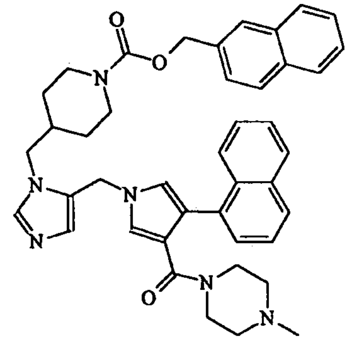
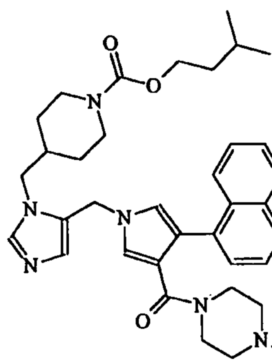
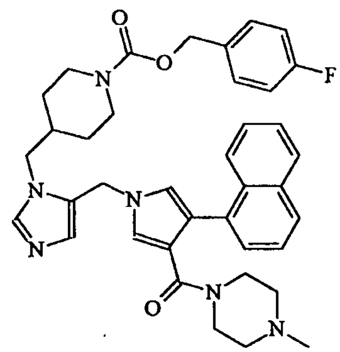
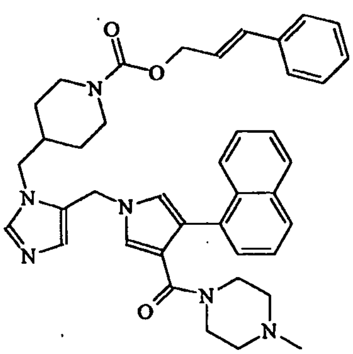
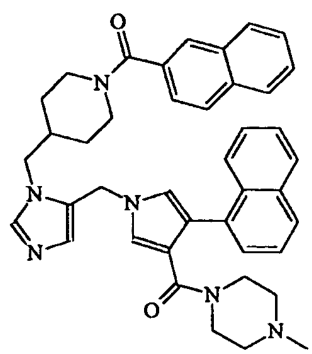
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
44		45	
46		47	
48		49	

Table 1-9

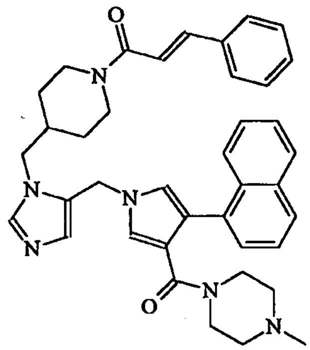
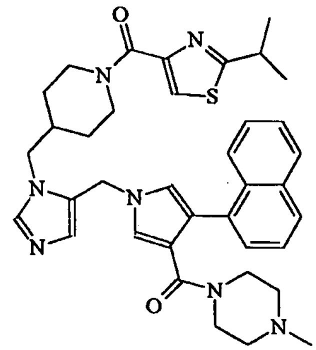
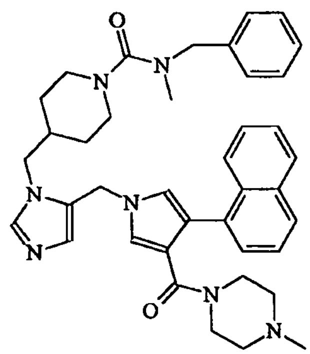
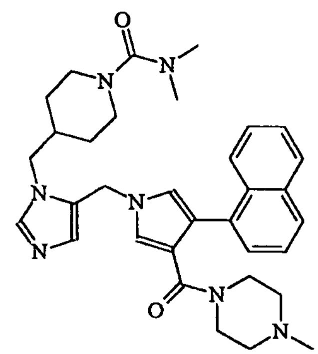
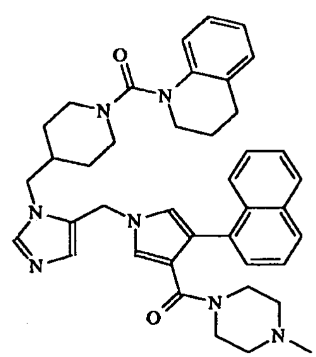
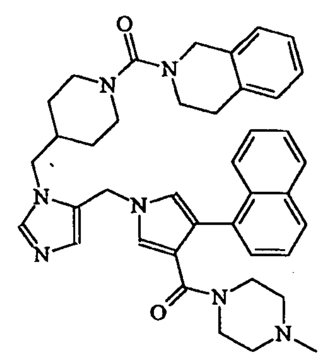
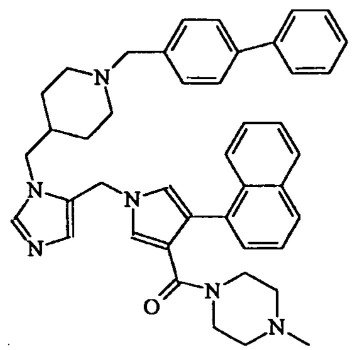
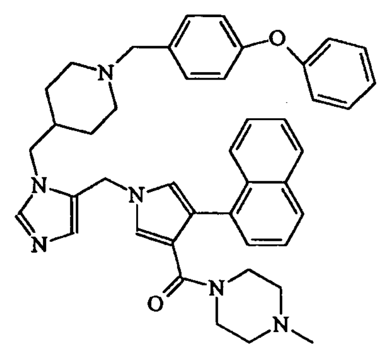
COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
50		51	
52		53	
54		55	

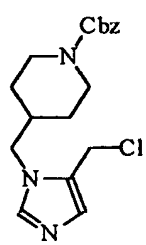
Table 1-10

COM. NO.	STRUCTURE	COM. NO.	STRUCTURE
56		57	

It is another object of the present invention to provide processes for preparing the piperidine derivative of formula (1) as defined above.

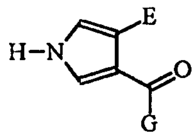
According to the present invention, the piperidine derivative of formula (1) can be prepared by a process characterized in that

(a) a compound represented by the following formula (2a):



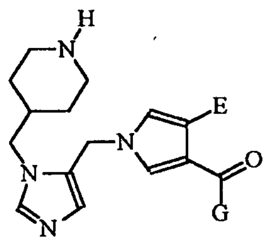
(2a)

wherein Cbz represents benzyloxycarbonyl and has the same meaning through the present specification, is reacted in a solvent in the presence of a base with a compound represented by the following formula (3):



(3)

wherein E and G are defined as previously described, then the protecting group Cbz is eliminated to produce a compound represented by the following formula (1a):



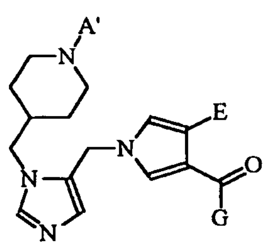
(1a)

wherein E and G are defined as previously described;

(b) the compound of formula (1a) is reacted in a solvent with a compound represented by the following formula (4):

A'—W (4)

wherein A' is the same with A except that A' is not hydrogen, and W represents hydrogen, hydroxy or reactive leaving group, preferably halogen, to produce a compound represented by the following formula (1b):



(1b)

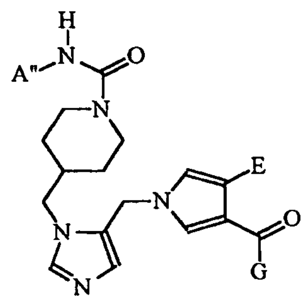
wherein A', E and G are defined as previously described;

(c) the compound of formula (1a) is reacted in a solvent with a

compound represented by the following formula (5):

A"—N=C=O (5)

wherein A" represents lower alkyl, benzyl or C_3-C_6-cycloalkyl, to produce a compound represented by the following formula (1c):



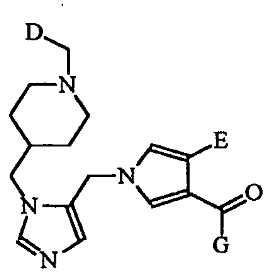
(1c)

wherein A", E and G are defined as previously described;

(d) the compound of formula (1a) is reacted in a solvent in the presence of a reducing agent with a compound represented by the following formula (6):

D–CHO (6)

wherein D is defined as previously described, to produce a compound represented by the following formula (1d):



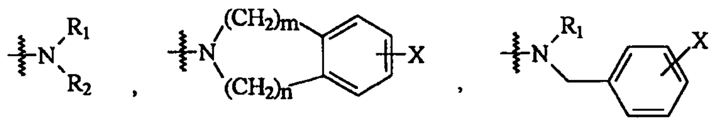
(1d)

wherein D, E and G are defined as previously described; or

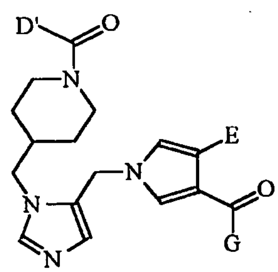
(e) the compound of formula (1a) is reacted in a solvent with phosgene and a compound represented by the following formula (7):

D'H (7)

wherein D' represents a radical selected from the following group:



wherein m, n, X, R_1 and R_2 are defined as previously described, to produce a compound represented by the following formula (1e):



(1e)

wherein D', E and G are defined as previously described.

However, the compound according to the present invention may be conveniently prepared by any methods designed by combining various synthetic ways known in the prior arts, and such combination can be easily performed by a person having ordinary skill in this art. The process variants (a) to (e) will be more specifically explained below.

In process variants (a) to (e) for preparing the compound according to the present invention, any inert solvent which does not adversely affect to the reaction, preferably one or more selected from a group consisting of dimethylformamide, dichloromethane, tetrahydrofuran, chloroform and dimethylacetamide can be used. As the base in process variant (a), one or more selected from a group consisting of sodium hydride, potassium t-butoxide, sodium bis(trimethylsilyl)amide and

potassium bis(trimethylsilyl)amide can be mentioned. Also, the deprotection reaction in process (a) to remove the benzyloxycarbonyl group at position-1 of piperidine ring may be carried out by applying the conventional reaction conditions, preferably by using $Pd(OH)_2/C$ or Pd/C in an alcohol solvent under hydrogen atmosphere.

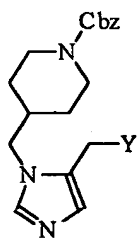
In process variant (b), the compound of formula (1a) obtained in process variant (a) is coupled with the compound of formula (4) in the solvent as mentioned above optionally in the presence of a tertiary amine base to produce the compound of formula (1b). When the compound of formula (4) wherein W is hydroxy is used, the reaction is preferably carried out in the presence of a coupling agent. As the coupling agent, a mixture of 1-hydroxybenzotrizole(HOBT) and one or more substances selected from a group consisting of carbodiimides such as dicyclohexylcarbodiimide(DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(EDC), 1,1'-dicarbonyldiimidazole(CDI), etc. can be mentioned.

The compound of formula (1) wherein B is C=O, D is lower alkyl, benzyl or amino substituted by C_3-C_6-cycloalkyl[=compound of formula (1c)] may be prepared by reacting the compound of formula (1a) obtained in process variant (a) with the isocyanate derivative of formula (5).

In process variant (d), a reductive amination reaction is carried out in the presence of a reducing agent. As the reducing agent which can be used in this reaction, those conventionally recognized as a weak reducing agent such as Pd/C under hydrogen atmosphere, sodium triacetoxyborohydride or sodium cyanoborohydride can be mentioned.

On the other hand, a compound represented by the following

formula (2) which includes the compound of formula (2a) used as a starting material in process variant (a) is a novel compound. Therefore, it is another object of the present invention to provide the compound of formula (2):

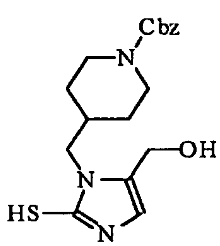


(2)

wherein Y represents hydroxy or chloro.

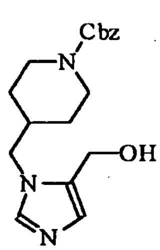
The novel intermediate of formula (2) can be prepared by processes characterized in that

(f) a compound represented by the following formula (8):



(8)

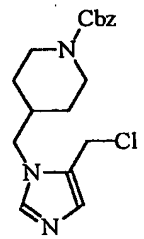
is desulfurated in an organic solvent in the presence of nitric acid to produce a compound represented by the following formula (2b):



(2b)

; or

(g) the compound of formula (2b) is reacted with thionyl chloride($SOCl_2$) to produce the compound of formula (2a):

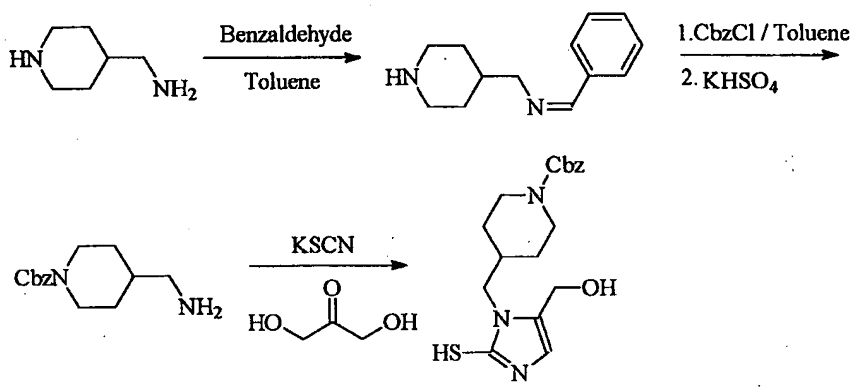


(2a

In order to desulfurate the compound of formula (8), 10% nitric acid is used in the present invention. At this time, a small quantity of organic solvent should be added to the reaction solution because of the solubility problem of the bulky benzyloxycarbonylpiperidine group. Ethyl acetate or tetrahydrofuran can be used as the organic solvent. However, it is also possible to prepare the compound of formula (2b) from the compound of formula (8) using the other processes known as desulfuration conditions. In addition, the compound of formula (2b) thus obtained may be reacted with thionyl chloride to effectively prepare the compound of formula (2a).

As depicted in Reaction Scheme 1 below, the compound of formula (8) used as a starting material in preparing the compound of formula (2) may be synthesized from 4-(aminomethyl)piperidine by a process, in which protection, benzyloxycarbonylation and deprotection to an amine compound, and then reaction with dihydroxyacetone in the presence of KSCN are included. *J. Med. Chem.*, 33, 1312-1329, 1990 in which a similar reaction is explained in detail can be referred to for the specific reaction conditions.

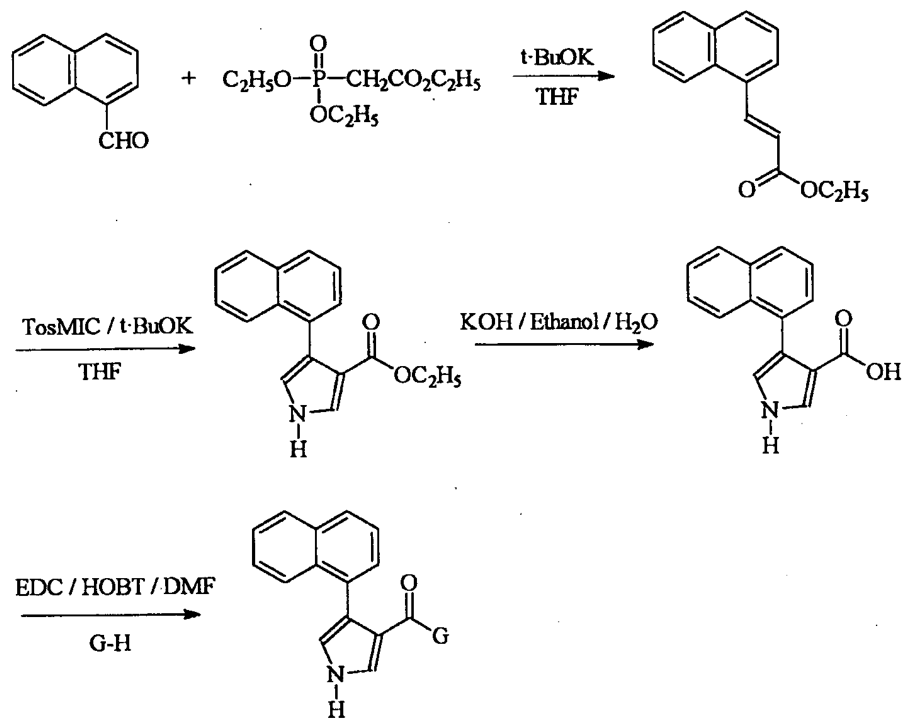
Reaction Scheme 1



in the above Reaction Scheme 1
CbzCl represents benzylchloroformate and has the same meaning through the present specification.

The compound of formula (3) used as a reactant in preparing the compound of formula (1) may be synthesized from 1-naphthaldehyde or 1-naphthoic acid as depicted in Reaction Scheme 2 below.

Reaction Scheme 2



in the above Reaction Scheme 2

TosMIC represents tosylmethylisocyanide and has the same meaning through the present specification.

The solvents which can be used in the first and second steps of Reaction Scheme 2 above include tetrahydrofuran, acetonitrile and dimethylformamide. As the base, one or more selected from a group consisting of potassium t-butoxide, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), potassium hydroxide and sodium hydroxide can be mentioned.

The reaction conditions including the amount of reactants, reaction temperature, reaction time, etc. in the processes according to the present invention can easily be determined by a person skilled in this art depending on the specific reactants.

In addition, the compound of formula (1) produced in the above processes in the form of a free base can easily be converted to a salt form as mentioned above according to the conventional methods known in this art.

After the reaction is completed, the resulting product may be further separated and/or purified by usual work-up processes, such as for example, chromatography, recrystallization, etc.

The compound of formula (1) prepared according to the processes above shows an inhibitory activity against farnesyl transferase, and thus can be effectively used as an anti-cancer agent. Therefore, the present invention also provides a pharmaceutical composition comprising the novel compound of formula (1), as defined above, or a pharmaceutically acceptable salt thereof as an active ingredient together with a pharmaceutically acceptable carrier. Particularly, the compound of formula (1) can be used very effectively for treating cancer, restenosis, atherosclerosis and infections from hepatitis delta and related viruses.

When the active compound according to the present invention is used for clinical purpose, it is preferably administered in an amount ranging from 5 to 200mg per kg of body weight a day. The total daily dosage may be administered in one time or over several times. However, the specific administration dosage for the patient can be varied with the specific compound used, body weight of the subject patient, sex, hygienic condition, diet, time or method of administration, excretion rate, mixing ratio of the agent, severity of the disease to be treated, etc.

The compound of the present invention may be administered in

the form of injections or oral preparations. Injections, for example, sterilized aqueous or oily suspension for injection, can be prepared according to the known procedure using suitable dispersing agent, wetting agent, or suspending agent. Solvents which can be used for preparing injections include water, Ringer's fluid and isotonic NaCl solution, and also sterilized fixing oil may be conveniently used as the solvent or suspending media. Any non-stimulative fixing oil including mono-, di-glyceride may be used for this purpose. Fatty acid such as oleic acid may also be used for injections.

As the solid preparation for oral administration, capsules, tablets, pills, powders and granules, etc., preferably capsules and tablets can be mentioned. It is also desirable for tablets and pills to be formulated into enteric-coated preparation. The solid preparations may be prepared by mixing the active compound of formula (1) according to the present invention with at least one carrier selected from a group consisting of inactive diluents such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agent and binding agent.

The present invention will be more specifically explained in the following examples. However, it should be understood that the following examples are intended to illustrate the present invention but not in any manner to limit the scope of the present invention. Processes for preparing the starting substances used for obtaining the compound of formula (1) will be also explained in detail in the following Preparations.

Preparation 1: Synthesis of 4-(5-chloromethyl-1H-imidazol-1-ylmethyl)-piperidine-1-carboxylic acid benzylester

1-1) 4-Aminomethyl-piperidine-1-carboxylic acid benzylester

22.2g(0.2 mol) of 4-aminomethyl-piperidine was dissolved in 250 mℓ of toluene and then 21.2g(0.2 mol) of benzaldehyde was added thereto. The mixture was refluxed for 3 hours with Dean-stack and cooled down to 0℃, and then 34.2g(0.2 mol) of benzylchloroformate was added dropwise thereto while stirring. After the mixture was stirred for 3 hours, 1N aqueous potassium hydrogen sulfate solution(220mℓ) was added thereto at room temperature. The mixture was extracted three times with 200mℓ of diethylether, and then the aqueous layer was basified with sodium hydroxide. The aqueous solution was saturated with sodium chloride and extracted three times with 100mℓ of dichloromethane. The organic solution was dried over magnesium sulfate and distilled under reduced pressure to obtain 38g(Yield 91%, Molecular weight 248) of the title compound.

^1H NMR($CDCl_3$) δ 1.11(s, 2H), 1.49(s, 3H), 1.70(d, 2H), 2.57 (d, 2H), 2.78(s, 2H), 4.20(s, 2H), 5.12(s, 2H), 7.34-7.35(m, 5H)

FAB(M+H): 249

1-2) 4-(5-Hydroxymethyl-2-mercapto-1H-imidazol-1-ylmethyl)-piperidine-1-carboxylic acid benzylester

24.8g(0.1 mol) of the compound prepared in Preparation 1-1) and 6.0g(0.1 mol) of acetic acid were dissolved in 50mℓ of isopropyl alcohol, and then the resulting solution was added to a solution wherein 12.6g(0.13 mol) of potassium thiocyanate, 9.0g(0.05 mol) of 1,3-dihydroxyacetone dimer and 10.0g(0.17 mol) of acetic acid were dissolved in 50mℓ of n-butanol. The whole mixture was stirred for 48 hours. The solvent was removed by distillation under reduced pressure, 200mℓ of ethyl acetate was added to the residue, and the mixture was washed three times with 100mℓ of water. The organic layer was dried over magnesium sulfate, and the solvent was removed by

distillation under reduced pressure to obtain 27g(75 mmol, Yield 75%, Molecular weight 361) of the title compound.

^1H NMR($CDCl_3$) δ 1.22(d, 2H), 1.57(d, 2H), 2.30(s, 1H), 2.72 (s, 2H), 3,96(s, 2H), 4.15(d, 2H), 4.46(s, 2H), 5.10(s, 2H), 6.62(s, 1H), 7.26-7.37(m, 5H)

FAB(M+H): 362

1-3) 4-(5-Hydroxymethyl-1H-imidazol-1-ylmethyl)-piperidine-1-carboxylic acid benzylester

18.05g(50 mmol) of the compound prepared in Preparation 1-2) was added to a mixture of 100mℓ of nitric acid(10%) and 10mℓ of ethyl acetate. The whole mixture was cooled down using ice water, and stirred at room temperature for 3 hours. The mixture was basified with 4N aqueous sodium hydroxide solution, and then extracted twice with 100mℓ of ethyl acetate. The organic extract was dried over magnesium sulfate and distilled under reduced pressure to obtain 12.3g (38 mmol, Yield 75%, Molecular weight 329) of the title compound.

^1H NMR($CDCl_3$) δ 1.16(d, 2H), 1.56(d, 2H), 1.98(s, 1H), 2.70 (s, 2H), 3,88(d, 2H), 4.18(s, 2H), 4.49(s, 1H), 4.52(br, 1H), 4.58(s, 2H), 5.10(s, 2H), 6.82(s, 1H), 7.27-7.40(m, 5H)

FAB(M+H): 330

1-4) 4-(5-Chloromethyl-1H-imidazol-1-ylmethyl)-piperidine-1-carboxylic acid benzylester

9.9g(30 mmol) of the compound prepared in Preparation 1-3) was dissolved in 50mℓ of chloroform, and 7.1g(60 mmol) of thionyl chloride was slowly added dropwise thereto at 0℃. The mixture was stirred for 2 hours, the solvent was removed by distillation under reduced pressure,

and the residual hydrochloric acid was removed under vacuum to obtain 9.9g(Yield 95%, Molecular weight 347.5) of hydrochloride salt of the title compound.

^{1}H NMR($CDCl_3$) δ 1.12(d, 2H), 1.53(d, 2H), 2.65(s, 2H), 3.82 (d, 2H), 4.22(s, 2H), 4.42(s, 1H), 4.49(s, 3H), 5.12(s, 2H), 6.60(s, 1H), 7.30-7.41(m, 5H)

FAB(M+H): 349

Preparation 2: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole

2-1) 3-(Naphthalen-1-yl)-acrylic acid ethylester

22.4g(0.10 mol) of triethylphosphonoacetate was dissolved in 500 mℓ of tetrahydrofuran and 12.4g(1.1 mol) of potassium t-butoxide was slowly added thereto. To this solution was slowly added 15.6g(0.10 mol) of 1-naphthaldehyde dissolved in 20mℓ of tetrahydrofuran, then the resulting solution was stirred for 8 hours. The organic solvent was eliminated by distillation under reduced pressure, and the residue was dissolved in ethyl acetate, washed twice with water, dried over magnesium sulfate and concentrated. The concentrate was subjected to silica gel column chromatography(eluent: n-hexane/ethyl acetate=95/5, v/v) to obtain 20.3g(0.090 mol, Yield 90%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.33(t, 3H), 4.10(q, 2H), 6.75(q, 1H), 7.50(m, 3H), 7.73(d, 1H), 7.85(m, 2H), 8.10(d, 1H), 8.21(d, 1H)

FAB 227 (M+H)

2-2) 3-(Ethoxycarbonyl)-4-(naphthalen-1-yl)-1H-pyrrole

5g(18.9 mmol) of 3-(naphthalen-1-yl)-acrylic acid ethyl ester

prepared in Preparation 2-1) and 3.68g(18.9 mmol) of tosylmethylisocyanide were dissolved in 100mℓ of tetrahydrofuran. To this solution was slowly added 2.55g(22.7 mmol) of potassium t-butoxide dissolved in 100mℓ of tetrahydrofuran, then the resulting solution was refluxed for 30 minutes. 100mℓ of water was added to the reaction solution in order to stop the reaction, and the solvent was eliminated under reduced pressure. The residue was extracted with diethylether, washed with aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography(eluent: ethyl acetate/n-hexane=1/3, v/v) to obtain 3.85g(14.5 mmol, Yield 77%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.27(t, 3H), 4.07(q, 2H), 6.76(s, 1H), 7.28-7.47(m, 5H), 7.59(s, 1H), 7.82(m, 2H), 9.99(s, 1H)

FAB 266 (M+H)

2-3) 3-Hydroxycarbonyl-4-(naphthalen-1-yl)-1H-pyrrole

2.64g(10 mmol) of the compound prepared in Preparation 2-2) was dissolved in 50mℓ of 50% ethanol, and 2.24g(40 mmol) of potassium hydroxide was added thereto. The reaction solution was refluxed for 7 hours, cooled down to room temperature, adjusted to pH 4-5, extracted with ethyl acetate and dried over sodium sulfate. The solvent was removed under reduced pressure to obtain 1.62g(8.1 mmol, Yield 81%) of the title compound. This compound was used in the next step reaction without purification.

^{1}H NMR($CDCl_3$) δ 6.60(s, 1H), 7.32-7.49(m, 5H), 7.54(s,1H), 7.84(m, 2H), 9.92(s, 1H)

FAB 238 (M+H)

2-4) 3-(Morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole

234mg(1 mmol) of the compound prepared in Preparation 2-3) was dissolved in 2mℓ of dimethylformamide, 230mg(1.2 mmol) of EDC and 162mg(1.7 mmol) of HOBT were added thereto, and the resulting mixture was stirred for 5 minutes at 0℃. 87mg(1 mmol) of morpholine was added to the reaction solution, which was then stirred for 5 hours at room temperature. The solvent was removed under reduced pressure and 10mℓ of saturated aqueous potassium carbonate solution was added to the residue. This solution was extracted with ethyl acetate, washed with 10mℓ of 1N aqueous hydrochloric acid solution, washed with aqueous sodium chloride solution and water, dried over sodium sulfate and then concentrated to obtain 243mg(0.8 mmol, Yield 80%) of the title compound.

^{1}H NMR($CDCl_3$) δ 2.13-3.52(br, 8H), 6.54(s, 1H), 7.31-7.51(m, 5H), 7.53 (s, 1H), 7.81(m, 2H), 9.93(s, 1H)

FAB 307 (M+H)

2-5) 3-[N-(2-Methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole

234mg(1 mmol) of the compound prepared in Preparation 2-3) was dissolved in 2mℓ of dimethylformamide, 230mg(1.2 mmol) of EDC, 101mg (1 mmol) of triethylamine and 162mg(1.7 mmol) of HOBT were added thereto, and the resulting mixture was stirred for 5 minutes at 0℃. 124mg(1 mmol) of N-(2-methoxyethyl)-N-methylamine hydrochloride was added to the reaction solution, which was then stirred for 5 hours at room temperature. The solvent was removed under reduced pressure and 10mℓ of saturated aqueous potassium carbonate solution was added to the residue. This solution was extracted with 20mℓ of ethyl acetate, washed with 10mℓ of 1N aqueous hydrochloric acid solution, washed

with aqueous sodium chloride solution and water, dried over sodium sulfate and then concentrated to obtain 246mg(0.8 mmol, Yield 80%) of the title compound.

^{1}H NMR($CDCl_3$) δ 2.46(s, 2H), 2.80-3.40(m, 8H), 3.40(s, 1H), 6.80(s, 1H), 7.00(s, 1H), 7.42(m, 4H), 7.73(d, 1H), 7.81(d, 1H), 8.17(d, 1H), 10.66 (s, 1H)

FAB 309 (M+H)

Preparation 3: Synthesis of 4-hydroxymethyl-2-(2-propyl)thiazole

3-1) 2-Methylpropionthioamide

3.0g(43 mmol) of isobutyronitrile was dissolved in a solvent mixture of 30mℓ of pyridine saturated with hydrogen sulfide gas and 9mℓ of triethylamine, and the resulting solution was stirred for 12 hours at room temperature. The solvent was removed under reduced pressure and then the residue was dissolved in 200mℓ of ethyl acetate and washed with 0.5N HCl and water. The organic layer was dried over anhydrous magnesium sulfate, concentrated and subjected to silica gel column chromatography(eluent: ethyl acetate/n-hexane=1/1, v/v) to obtain 3.1g(30 mmol, Yield 70%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.26(d, 3H), 1.28(d, 3H), 2.92(m, 1H), 7.38(br, 1H), 8.32(br, 1H)

3-2) 4-Ethoxycarbonyl-2-(2-propyl)thiazole

3.0g(29 mmol) of the compound prepared in Preparation 3-1) and 5.6g(29 mmol) of ethyl bromopyruvate were dissolved in 50mℓ of ethanol and the resulting mixture was refluxed for 3 hours. The solvent was removed under reduced pressure and the residue was subjected to column

chromatography(eluent: ethyl acetate/n-hexane=1/4, v/v) to obtain 4.5g(23 mmol, Yield 79%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.31-1.35(m, 9H), 3.34(m, 1H), 4.35(q, 2H), 8.11(s, 1H)

3-3) 4-Hydroxymethyl-2-(2-propyl)thiazole

95mg(2.5 mmol) of lithium aluminum hydride was added to 3mℓ of tetrahydrofuran at 0℃ and 500mg(2.51 mmol) of the compound prepared in Preparation 3-2) was slowly added thereto. The resulting mixture was stirred for 10 minutes at room temperature and 10mℓ of water was carefully added thereto. This solution was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated, and then the concentrate was subjected to column chromatography(eluent: ethyl acetate/n-hexane=7/3, v/v) to obtain 220mg(1.40 mmol, Yield 56%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.34(d, 3H), 1.36(d, 3H), 3.27(m, 1H), 4.71(s, 2H), 5.22(s, 1H), 7.03(s, 1H)

Preparation 4: Synthesis of 2-(2-propyl)thiazole-4-carboxylic acid

200mg(1.00 mmol) of the compound prepared in Preparation 3-2) was dissolved in a solvent mixture of tetrahydrofuran, methanol and water(1.0mℓ/0.6mℓ/0.3mℓ) and 63mg(1.5 mmol) of lithium hydroxide was added thereto. This reaction mixture was stirred for 1 hour at room temperature and the solvent was removed under reduced pressure. Water was added to the residue, which was then adjusted to about pH 6 using diluted aqueous hydrochloric acid solution and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate

and concentrated to obtain 130mg(1.40 mmol, Yield 76%) of the title compound. This compound was used in the next step reaction without further purification.

^{1}H-NMR($CDCl_3$+CD_3OD) δ 1.25(m, 6H), 3.30(m, 1H), 8.05(s, 1H)

Preparation 5: Synthesis of 3-(naphthalen-1-yl)carbonyl-1H- pyrrole

5-1) Methyl N-methyl-1-naphthalene hydroxamate

3.44g(20 mmol) of 1-naphthoic acid was dissolved in 20mℓ of dimethylformamide. To this solution were added 4.6g(24 mmol) of EDC, 2.02g(20 mmol) of triethylamine and 3.24g(24 mmol) of HOBT, and the resulting mixture was stirred for 5 minutes at 0℃. 1.85mg(20 mmol) of N,O-dimethylhydroxylamine hydrochloride was added thereto, and the mixture was stirred for 5 hours at room temperature. The solvent was removed under reduced pressure, 100mℓ of saturated aqueous K_2CO_3 solution was added to the residue, which was then extracted with ethyl acetate. The organic layer was sequencially washed with 1N aqueous hydrochloric acid solution, aqueous sodium chloride solution and water, dried over anhydrous sodium sulfate and concentrated to obtain 3.04g(1.50 mmol) of the title compound.

^{1}H NMR($CDCl_3$) δ 2.42(s, 3H), 3.24(s, 3H), 7.47(m, 4H), 7.67(d, 1H), 7.74(m, 2H),

FAB 216 (M+H)

5-2) 1-(Naphthalen-1-yl)-prop-2-en-1-one

2.03g(9.4 mmol) of the compound prepared in Preparation 5-1) was dissolved in 20mℓ of dry tetrahydrofuran, and 20mℓ of 1N

vinylmagnesiumbromide-tetrahydrofuran solution was slowly added thereto at 0℃. The mixture was stirred for 30 minutes at room temperature, 20mℓ of 1N hydrochloric acid was added thereto, and the resulting mixture was extracted with 50mℓ of ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent therein was removed under reduced pressure to obtain 1.63g(9 mmol, Yield 96%) of the title compound.

^{1}H NMR($CDCl_3$) δ 6.92(m, 1H), 7.51(m, 4H), 7.74(d, 1H), 7.85(m, 2H), 7.98(d, 1H), 8.31(d, 1H)

5-3) 3-(Naphthalen-1-yl)carbonyl-1H-pyrrole

901mg(5 mmol) of the compound prepared in Preparation 5-2) and 1.01g(5.5 mmol) of tosylmethylisocyanide were dissolved in 10mℓ of tetrahydrofuran, and then 555mg(5.5 mmol) of potassium t-butoxide in tetrahydrofuran(10mℓ) was slowly added thereto. The reaction solution was stirred for 30 minutes and 10mℓ of water was added to the solution in order to stop the reaction. The solvent was removed under reduced pressure. 20mℓ of water was added to the residue, which was then extracted with ethyl acetate, washed with aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to column chromatography(eluent: ethyl acetate/n-hexane=1/3, v/v) to obtain 884mg(4 mmol, Yield 80%) of the title compound.

^{1}H NMR($CDCl_3$) δ 6.57(s, 1H), 6.66(s, 1H), 6.79(s, 1H), 7.36(m, 3H), 7.48(d, 1H), 7.77(d, 1H), 7.82(d, 1H), 8.04(d, 1H), 9.91(s, 1H)

Example 1: Synthesis of 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl methyl)-1H-imidazol-5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthale

n-1-yl)-1H-pyrrole(1)

612mg(2.0 mmol) of the compound prepared in Preparation 2-4) was dissolved in 10mℓ of dimethylformamide, 264mg(6.6 mmol) of sodium hydride(60%) was added thereto at 0℃, and then the resulting mixture was stirred for 5 minutes. To this mixture was added 765mg (2.2 mmol) of the compound prepared in Preparation 1-4) and the whole mixture was stirred for 5 hours at room temperature. The solvent was removed by distillation under reduced pressure and 10mℓ of water was added to the residue. The resulting mixture was extracted twice with 20mℓ of ethyl acetate, dried over magnesium sulfate, concentrated and subjected to silica gel column chromatography(eluent: dichloromethane/ methanol=90/10, v/v) to obtain 930mg(Yield 75 %) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.11(d, 2H), 1.51(m, 3H), 2.30(br, 1H), 2.54-3.41(br, 9H), 3.75(d, 2H), 4.18(s, 2H), 5.10(s, 2H), 5.18(s, 2H), 6.75(s, 1H), 7.18(s, 1H), 7.20-7.53(m, 10H), 7.71(s, 1H), 7.82(d, 1H), 7.88(d, 1H), 8.07(d, 1H)

FAB (M+H) 618

Example 2: Synthesis of 3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1-[1-(piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(2)

227mg(0.36 mmol) of the compound prepared in Example 1 was dissolved in 5mℓ of methanol, 20mg of palladium hydroxide carbon ($Pd(OH)_2/C$) was added thereto, and the mixture was reacted for 2 hours under 1 atm of hydrogen gas. The reactants were filtered and the solvent was removed. The residue was subjected to silica gel column chromatography(eluent: ammonia water/methanol=15/85, v/v) to obtain 120 mg(0.26 mmol, Yield 74%) of the title compound.

[1]H NMR(CD_3OD) δ 1.07(m, 2H), 1.25-1.48(m, 3H), 2.25(br, 3H), 2.40(m, 2H), 2.60-3.40(m, 8H), 3.78(d, 2H), 5.22(s, 2H), 6.88(s, 1H), 7.12(d, 2H), 7.26(m, 1H), 7.35 (m, 3H), 7.63(s, 1H), 7.75(d, 1H), 7.80(d, 1H), 7.93(d, 1H)

FAB (M+H) 484

Example 3: Synthesis of 1-[1-(1-acetylpiperidin-4-ylmethyl)-1H-imidazol -5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole (3)

30mg(62 μmol) of the compound prepared in Example 2 was added to 2mℓ of dichloromethane and then 5.4mg(6.9 μmol) of acetyl chloride was added thereto using a syringe. The mixture was reacted for 2 hours. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=80/20, v/v) to obtain 26mg(5.3 μmol, Yield 85%) of the title compound.

[1]H NMR($CDCl_3$+CD_3OD) δ 1.09-1.35(m, 3H), 1.45-1.75(m, 4H), 2.08(s, 3H), 2.10(br, 1H), 2.30(br, 1H), 2.44(t, 1H), 2.96(t, 2H), 3.08(br, 2H), 3.30(br, 1H), 3.79(d, 1H), 3.89(d, 2H), 4.55(d, 1H), 5.25(s, 2H), 6.80(s, 1H), 7.18(s, 1H), 7.28-7.52(m, 5H), 7.83(d, 1H), 7.99(d, 1H), 8.01(d, 1H), 8.06(s, 1H)

FAB (M+H) 526

Example 4: Synthesis of 1-[1-(1-methylsulfonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(4)

30mg(62 μmol) of the compound prepared in Example 2 was added to 2mℓ of dichloromethane and then 7.8mg(6.9 μmol) of methyl sulfonylchloride was added thereto using a syringe. The mixture was reacted for 2 hours. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (eluent: dichloromethane/methanol=90/10, v/v) to obtain 25mg(4.6 μmol, Yield 85%) of the title compound.

^{1}H NMR($CDCl_3$+CD_3OD) δ 1.08(m, 2H), 1.35-1.65(m, 3H), 2.25(br, 2H), 2.45(t, 2H), 2.65(s, 3H), 2.75-3.40(br, 6H), 3.54(d, 2H), 3.82(d, 2H), 5.23(s, 2H), 6.91(s, 1H), 7.14(m, 2H), 7.26(d, 1H), 7.32-7.50(m, 3H), 7.68(s, 1H), 7.76(d, 1H), 7.82(d, 1H), 7.93(d, 1H)

FAB (M+H) 562

Example 5: Synthesis of 1-[1-(1-benzyloxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(5)

616mg(2.0 mmol) of the compound prepared in Preparation 2-5) was dissolved in 10mℓ of dimethylformamide, 264mg(6.6 mmol) of sodium hydride (60%) was added thereto at 0℃, and then the resulting mixture was stirred for 5 minutes. 765mg(2.2 mmol) of the compound prepared in Preparation 1-4) was added to the mixture and the whole mixture was stirred for 5 hours at room temperature. The solvent was removed by distillation under reduced pressure and 10mℓ of water was added to the residue. This solution was extracted twice with 20mℓ of ethyl acetate, dried over magnesium sulfate, concentrated, and then subjected to silica gel column chromatography(eluent: dichloromethane/methanol=90/10, v/v) to obtain 930mg(Yield 75 %) of the title compound.

[1]H NMR($CDCl_3$) δ 1.11(s, 2H), 1.35-1.65(m, 3H), 2.39(s, 2H), 2.70(br, 4H), 2.90-3.20(m, 5H), 3.32(s, 1H), 3.78(d, 2H), 4.16(br, 2H), 5.08(s, 2H), 5.16 (s, 2H), 6.74(s, 1H), 7.10(s, 1H), 7.21-7.50(m, 10H), 7.76(d, 1H), 7.84(d, 1H), 7.91(s, 1H), 8.07(d, 1H)

FAB (M+H) 620

Example 6: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(6)

227mg(0.36 mmol) of the compound prepared in Example 5 was dissolved in 5mℓ of methanol, 20mg of palladium hydroxide carbon was added thereto, and then the resulting mixture was reacted for 2 hours under 1 atm of hydrogen gas. The reactants were filtered, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: ammonia water/methanol=15/85, v/v) to obtain 128 mg(0.26 mmol, Yield 74%) of the title compound.

[1]H NMR($CDCl_3$) δ 1.10-1.30(br, 3H), 1.47(d, 2H), 2.30-2.60(m, 4H), 2.68(br, 1H), 2.90-3.18(m, 6H), 3.29(s, 1H), 3.63(m, 2H), 4.04(br, 2H), 5.06(s, 2H), 6.71(s, 1H), 7.04(s, 1H), 7.12(s, 1H), 7.26-7.57(m, 5H), 7.71(d, 1H), 7.79(d, 1H), 8.05(d, 1H)

FAB (M+H) 486

Example 7: Synthesis of 1-[1-(1-acetyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(7)

30mg(62 μmol) of the compound prepared in Example 6 was added to 2mℓ of dichloromethane, and 5.4mg(6.9 μmol) of acetyl

chloride was added thereto using a syringe. The resulting mixture was reacted for 2 hours, the solvent was removed under reduced pressure, and then the residue was subjected to silica gel column chromatography (eluent: dichloromethane/methanol=80/20, v/v) to obtain 27.8mg(5.3 μmol, Yield 85%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.05-1.35(br, 3H), 1.51(m, 3H), 2.04(s, 3H), 2.41(br, 3H), 2.72(br, 1H), 2.88-3.22(m, 6H), 3.33(br, 1H), 3.75(d, 1H), 4.01(d, 2H), 4.58(d, 1H), 5.28(s, 2H), 6.79(s, 1H), 7.18(s, 1H), 7.25-7.55(m, 5H), 7.78(d, 1H), 7.86(d, 1H), 8.09(d, 1H), 8.78(s, 1H)

FAB (M+H) 528

Example 8: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-1-[1-(1-methylsulfonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-4-(naphthalen-1-yl)-1H-pyrrole(8)

30mg(62 μmol) of the compound prepared in Example 6 was added to 2mℓ of dichloromethane, and 7.8mg(6.9 μmol) of methylsulfonyl chloride was added thereto using a syringe. The resulting mixture was reacted for 2 hours, the solvent was removed under reduced pressure, and then the residue was subjected to silica gel column chromatography (eluent: dichloromethane/methanol=90/10, v/v) to obtain 26mg(4.6 μmol, Yield 85%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.25(br, 4H), 1.55(br, 2H), 2.43(br, 4H), 2.70(s, 3H), 2.81-3.24(m, 6H), 3.34(br, 1H), 3.68(d, 2H), 4.04(d, 2H), 5.27(s, 2H), 6.80(s, 1H), 7.15(s, 1H), 7.25-7.55(m, 5H), 7.78(d, 1H), 7.87(d, 1H), 8.05(d, 1H), 8.64(s, 1H)

FAB (M+H) 564

Example 9: Synthesis of 1-{1-[1-(N-benzylcarbamoyl)-piperidin-4-yl methyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(9)

62mg(128 μmol) of the compound prepared in Example 6 was added to 2mℓ of dichloromethane, and 20.5mg(153 μmol) of benzyl isocyanate was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 62mg(Yield 78%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.01(br, 2H), 1.30-1.51(m, 3H), 2.42(s, 1H), 2.50-2.72 (m, 6H), 2.90-3.10(m, 6H), 3.30(s, 1H), 3.42(s, 3H), 3.30(d, 1H), 4.92(d, 2H), 5.25(br, 1H), 6.72(s, 1H), 7.01(s, 1H), 7.15-7.30(m, 7H), 7.55(m, 3H), 7.60(s, 1H), 7.75(d, 1H), 7.85(d, 1H), 8.07(d, 1H)

FAB (M+H) 619

Example 10: Synthesis of 1-{1-[1-(N-butylcarbamoyl)-piperidin-4-yl methyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(10)

62mg(128 μmol) of the compound prepared in Example 6 was added to 2mℓ of dichloromethane, and 15mg(153 μmol) of butyl isocyanate was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 61mg(Yield 85%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.91(t, 3H), 1.07(s, 2H), 1.57(m, 4H), 2.55(br, 2H), 2.61(br, 2H), 2.71-2.90(m, 1H), 3.0-3.25(m, 8H), 3.31(br,

1H), 3.40(m, 3H), 3.73(br, 2H), 3.95(m, 2H), 4.85(br, 1H), 5.15(s, 2H), 6.71(s, 1H), 7.11(s, 1H), 7.35(m, 5H), 7.74(d, 1H), 7.85(d, 1H), 7.91(s, 1H), 8.07(s, 1H)

FAB (M+H) 585

Example 11: Synthesis of 1-{1-[1-(N-cyclohexylcarbamoyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(11)

62mg(128 μmol) of the compound prepared in Example 6 was added to 2mℓ of dichloromethane, and 19mg(153 μmol) of cyclohexyl isocyanate was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 49mg(Yield 65%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.09(m, 5H), 1.35(m, 3H), 1.45(dd, 2H), 1.60(dd, 1H), 1.67(dd, 2H), 1.82(dd, 2H), 2.42(t, 2H), 2.50-2.80(m, 3H), 2.90-3.20(m, 3H), 3.37(br, 1H), 3.50(s, 3H), 3.61(m, 1H), 3.72(d, 2H), 3.90(dd, 2H), 4.51(br, 1H), 5.18(s, 2H), 6.72(s, 1H), 7.08(s, 1H), 7.22(s, 1H), 7.31(t, 1H), 7.55 (br, 3H), 7.61(s, 1H), 7.75(d, 1H), 7.86(d, 1H), 8.08(d, 1H)

FAB (M+H) 611

Example 12: Synthesis of 1-[1-(1-heptanoyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(12)

62mg(128 μmol) of the compound prepared in Example 6 was dissolved in 2mℓ of dichloromethane, and 19mg(128 μmol) of heptanoyl

chloride was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 31mg(Yield 40%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.90(t, 5H), 1.04(m, 2H), 1.20-1.40(br, 7H), 1.50-1.70 (br, 4H), 2.19(t, 2H), 2.30(t, 2H), 2.41(br, 1H), 2.71(br, 1H), 2.75-3.10(m, 4H), 3.12(s, 1H), 3.35(s, 1H), 3.70(s, 2H), 3.81(d, 1H), 4.60(d, 1H), 5.12(s, 2H), 6.75(s, 1H), 7.10(s, 1H), 7.21(s, 1H), 7.31(t, 1H), 7.40-7.50(m, 3H), 7.61(s, 1H), 7.75(d, 1H), 7.85(d, 1H), 8.07 (d, 1H)

FAB (M+H) 598

Example 13: Synthesis of 1-{1-[1-(4-methoxybenzylcarbonyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(13)

62mg(128 μmol) of the compound prepared in Example 6 was dissolved in 2mℓ of dichloromethane, and 23mg(128 μmol) of 4-methoxyphenylacetyl chloride was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 50mg(Yield 62%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.78(m, 1H), 1.07(m, 1H), 1.30(br, 1H), 1.40(dd, 1H), 1.51(dd, 1H), 2.40(br, 3H), 2.72(br, 1H), 2.85(br, 1H), 2.85-3.10(m, 3H), 3.17(br, 1H), 3,31(br, 1H), 3.40-3.75(m, 5H), 3.75-3.90(m, 5H), 4.48(d, 1H), 5.09(s, 2H), 6.71(s, 1H), 6.81(m, 2H), 7.02-7.15(m, 3H), 7.21(br, 1H), 7.31 (br, 1H), 7.35-7.45(m, 3H), 7.56(s,

1H), 7.75(d, 1H), 7.85(d, 1H), 8.08(d, 1H)

FAB (M+H) 634

Example 14: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(1-phenoxyacetyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(14)

62mg(128 μmol) of the compound prepared in Example 6 was dissolved in 2mℓ of dichloromethane, and 23mg(128 μmol) of phenoxy-acetyl chloride was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 50mg(Yield 63%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.10(m, 2H), 1.40(br, 1H), 1.57(m, 2H), 2.40(br, 3H), 2.70(br, 1H), 2.90-3.20(m, 7H), 3.31(br, 1H), 3.85(br, 2H), 3.98(d, 1H), 4.50 (d, 1H), 4.61(m, 2H), 5.21(s, 2H), 6.70(s, 1H), 6.87(d, 2H), 6.98(t, 1H), 7.17(s, 1H), 7.20-7.40(m, 4H), 7.40-7.50(m, 3H), 7.70(d, 1H), 7.73(d, 1H), 8.10(d, 1H), 8.14(s, 1H)

FAB (M+H) 620

Example 15: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(2-phenylethylcarbonyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(15)

62mg(128 μmol) of the compound prepared in Example 6 was dissolved in 2mℓ of dichloromethane, and 22mg(128 μmol) of 3-phenyl-propionyl chloride was added thereto. The resulting mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/

methanol=95/5, v/v) to obtain 49mg(Yield 63%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.80(m, 1H), 1.01(m, 1H), 1.31(br, 1H), 1.42(d, 1H), 1.52(d, 1H), 2.35(m, 3H), 2.60(m, 2H), 2.51(t, 1H), 2.78(br, 1H), 2.80(m, 1H), 2.90-3.01(m, 4H), 3.01(s, 2H), 3.11(s, 1H), 3.31(br, 1H), 3.60-3.81(m, 3H), 4.61(d, 1H), 5.15(s, 2H), 6.75(s, 1H), 7.12(s, 1H), 7.15-7.35(m, 7H), 7.45-7.50(m, 3H), 7.71(s, 1H), 7.79(d, 1H), 7.81(d, 1H), 8.08(d, 1H)

FAB (M+H) 618

Example 16: Synthesis of 1-{1-[1-(4-biphenylacetyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(16)

62mg(128 μmol) of the compound prepared in Example 6 was dissolved in 2mℓ of dimethylformamide, to which were added 27mg(128 μmol) of 4-biphenylacetic acid, 14mg(128 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and 17mg(128 mmol) of N-hydroxybenzotriazole. The resulting mixture was reacted for 3 hours, the solvent was removed, and then 10mℓ of ethyl acetate was added to the residue. The resulting solution was washed twice with 10mℓ of water and further washed with 10mℓ of 6N aqueous sodium hydrogen carbonate solution. The solvent was removed under reduced pressure and the residue was subjected to silica gel column chromatography (eluent: dichloromethane/methanol=95/5, v/v) to obtain 49mg(Yield 62%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.80(m, 1H), 1.10(m, 1H), 1.30(m, 1H), 1.42(d, 1H), 1.55(d, 1H), 2.35(m, 3H), 2.75(br, 1H), 2.85-3.24(m, 7H), 3.32(br, 1H), 3.60-3.80(m, 4H), 3.90(d, 1H), 4.61(d, 1H), 5.12(s, 2H),

6.72(s, 1H), 7.01(s, 1H), 7.20(s, 1H), 7.30(d, 2H), 7.32(t, 1H), 7.40-7.50(m, 5H), 7.50-7.60(m, 5H), 7.70(s, 1H), 7.72(d, 1H), 7.78(d, 1H), 8.09(d, 1H)

FAB (M+H) 680

Example 17: Synthesis of 1-[1-(1-methoxycarbonyl-piperidin-4-yl methyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbam oyl-4-(naphthalen-1-yl)-1H-pyrrole(17)

The title compound was obtained in a yield of 85% according to the same procedure as Example 7 except that methoxycarbonyl chloride was used instead of acetyl chloride.

^{1}H NMR($CDCl_3$) δ 1.05(br, 2H), 1.32(br, 1H), 1.53(br, 2H), 2.31-2.72(m, 5H), 3.03~3.33(m, 7H), 3.62(s, 3H), 3.66(m, 2H), 4.13(br, 2H), 5.12(s, 2H), 6.71(s, 1H), 7.03(s, 1H), 7.14(s, 1H), 7.24-7.43(m, 5H), 7.74(d, 1H), 7.82 (d, 1H), 8.10(d, 1H)

FAB (M+H) 544

Example 18: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(1-propionyl-piperidin-4-ylmethyl)-1H-imidazol-5 -ylmethyl]-1H-pyrrole(18)

The title compound was obtained in a yield of 82% according to the same procedure as Example 7 except that propionyl chloride was used instead of acetyl chloride.

^{1}H NMR($CDCl_3$) δ 1.12(m, 5H), 1.40(m, 1H), 1.61(m, 2H), 2.35(q, 2H), 2.41(m, 3H), 2.70(br, 1H), 2.85(m, 1H), 3.02(m, 5H), 3.17(br, 1H), 3.31(br, 1H), 3.75(m, 3H), 4.55(m, 1H), 5.17(s, 2H), 6.69(s,

1H), 7.09(s, 1H), 7.41 (m, 5H), 7.74(d, 1H), 7.83(d, 1H), 7.89(s, 1H), 8.05(d, 1H)

FAB (M+H) 542

Example 19: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-1-ylmethyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(19)

1.19g(7.52 mmol) of 1-naphthalene-methanol was dissolved in 15 mℓ of toluene and 1.04g(7.53 mmol) of potassium carbonate was added thereto. To this solution was added 3.89mℓ(1.93M in toluene) of phosgene solution at 0℃, and the whole solution was stirred for 2 hours at room temperature. The reactants were filtered to remove solid materials and then 0.108g(0.222 mmol) of the compound prepared in Example 6 and 0.046mℓ(0.33 mmol) of triethylamine were added thereto. The resulting mixture was stirred for 1 hour at room temperature, and distilled under reduced pressure to remove the solvent. 10mℓ of saturated aqueous sodium bicarbonate solution was added to the residue, which was then extracted with ethyl acetate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was subjected to column chromatography (eluent: dichloromethane/methanol=95/5, v/v) to obtain 65mg(0.097 mmol, Yield 44%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.10(br, 2H), 1.50(br, 2H), 2.36(s, 2H), 2.58-2.85(br, 4H), 2.90-3.23(br, 6H), 3.31(s, 1H), 3.70(s, 2H), 4.08(br, 1H), 4.25(br, 1H), 5.12(s, 2H), 5.51(s, 2H), 6.70(s, 1H), 7.04(s, 1H), 7.18(s, 1H), 7.29(m, 1H), 7.38-7.65(m, 7H), 7.70(s, 1H), 7.75(d, 1H), 7.79-7.95 (m, 3H), 8.00(d, 1H), 8.07(d, 1H)

FAB (M+1) 670

Examples 20 to 26

The compounds physico-chemical data of which are represented in the following Table 2 were obtained according to the same procedure as Example 19.

Table 2-1

COM. NO.	^{1}H-NMR($CDCl_3$)	FAB (M+1)
20	1.08(br, 2H), 1.61(br, 2H), 2.41(s, 2H), 2.71(br, 4H), 2.95-3.25 (br, 6H), 3.30(br, 1H), 3.69(d, 2H), 4.15(br, 2H), 5.07(s, 2H), 5.24(s, 2H), 6.68(s, 1H), 7.08(s, 1H), 7.20(s, 1H), 7.31(m, 1H), 7.40-7.60(m, 6H), 7.66(s, 1H), 7.73-7.97(m, 6H), 8.12(d, 1H)	670
21	1.15(m, 2H), 1.62(m, 10H), 2.10(m, 5H), 2.42(s, 2H), 2.71(br, 4H), 3.04(s, 4H), 3.14(s, 2H), 3.35(s, 1H), 3.76(d, 2H), 4.17(br, 2H), 4.59(s, 2H), 5.10(m, 1H), 5.19(s, 2H), 5.32(m, 1H), 7.10(s, 1H), 7.23(s, 1H), 7.36(m, 1H), 7.42(m, 3H), 7.75(s, 1H), 7.80(m, 2H), 7.86(d, 1H), 8.10(d, 1H)	666
22	1.04(m, 2H), 1.30-1.60(m, 4H), 1.64(s, 3H), 1.70(s, 3H), 2.38(br, 2H), 2.58(br, 2H), 2.67(br, 1H), 2.99(s, 3H), 3.08(br, 2H), 3.29(br, 1H), 3.66(d, 2H), 4.07(br, 2H), 4.50(d, 2H), 5.08(s, 2H), 5.20-5.30(m, 1H), 6.69(s, 1H), 7.03(s, 1H), 7.15(s, 1H), 7.29-7.55 (m, 5H), 7.52(d, 1H), 7.80(d, 1H), 8.04(d, 1H)	598
23	0.89(d, 6H), 1.06(d, 2H), 1.35-1.80(m, 6H), 2.39(br, 2H), 2.50-2.89(br, 3H), 2.90-3.20(br, 5H), 3.31(br, 1H), 3.71(d, 2H), 3.90 (br, 1H), 4.00-4.25(m, 4H), 5.12(s, 2H), 6.71(s, 1H), 7.08(s, 1H), 7.20(s, 1H), 7.38(d, 1H), 7.40(m, 3H), 7.73(s, 1H), 7.75(d, 1H), 7.80(d, 1H), 8.05(d, 1H)	600
24	1.38(br, 6H), 2.64(br, 9H), 3.68(br, 2H), 3.74(d, 2H), 4.12 (br, 2H), 5.02(s, 2H), 5.13(s, 2H), 6.72(s, 1H), 7.01(m, 4H), 7.39(m, 6H), 7.74(m, 2H), 7.83(d, 1H), 8.05(d, 1H)	638

Table 2-2

COM. NO.	^{1}H-NMR($CDCl_3$)	FAB (M+1)
25	1.11(br, 3H), 1.51(d, 2H), 3.01(br, 12H), 3.74(d, 2H), 4.14(s, 2H), 4.68(s, 2H), 5.13(s, 2H), 6.25(m, 1H), 6.56(d, 1H), 6.73(s, 1H), 7.08(s, 1H), 7.15-7.65(m, 10H), 7.73(d, 1H), 7.77(s, 1H), 7.82(d, 1H), 8.06(d, 1H)	646
26	1.24(m, 2H), 1.33(m, 6H), 1.38(m, 2H), 1.53(m, 2H), 2.41(m, 2H), 2.76(m, 2H), 3.01-3.32(m, 8H), 3.43(m, 2H), 3.69(m, 2H), 4.15(m, 2H), 5.11(s, 2H), 6.73(s, 1H), 7.06(s, 1H), 7.19(s, 1H), 7.25-7.45(m, 5H), 7.65(s, 1H), 7.77(d, 1H), 7.83(d, 1H), 8.09(d, 1H)	669

Example 27: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(27)

100mg(0.206 mmol) of the compound prepared in Example 6 and 39mg(0.22 mmol) of 2-naphthoic acid were dissolved in 1mℓ of dimethylformamide, 59mg(0.31 mmol) of EDC and 42mg(0.31 mmol) of HOBT were added thereto, and then the mixture was stirred for 2 hours at room temperature. The solvent was removed by distillation under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and subjected to column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 83mg(0.13 mmol, Yield 63%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.16(br, 2H), 1.60(br, 2H), 2.40(br, 2H), 2.60-3.23(m, 9H), 3.31(br, 1H), 3.71(s, 3H), 4.45(br, 1H), 4.70(br, 1H),

5.10(s, 2H), 6.72(d, 1H), 7.04(s, 1H), 7.17(s, 1H), 7.31(d, 1H), 7.35-7.55 (m, 6H), 7.58(s, 1H), 7.73(d, 1H), 7.75-7.95(m, 5H), 8.04(d, 1H)

FAB (M+1) 640

Examples 28 to 29

The compounds physico-chemical data of which are represented in the following Table 3 were obtained according to the same procedure as Example 27 except that trans-cinnamic acid and 2-(2-propyl)thiazole-4-carboxylic acid, respectively, were used instead of 2-naphthoic acid.

Table 3

COM. NO.	^{1}H-NMR($CDCl_3$)	FAB (M+1)
28	1.06(s, 2H), 1.37(s, 1H), 1.55(d, 2H), 2.25-2.60(br, 4H), 2.70(br, 1H), 2.90-3.2(br, 6H), 3.30(br, 1H), 3.68(s, 2H), 4.06(m, 1H), 4.65(s, 1H), 5.10(s, 2H), 6.73(s, 1H), 6.83 (d, 1H), 7.04(s, 1H), 7.17(s, 1H), 7.25-7.52(m, 9H), 7.56(s, 2H), 7.71(d, 1H), 7.80(d, 1H), 8.07(d, 1H)	616
29	1.22(m, 2H), 1.34(d, 3H), 1.36(d, 3H), 1.38(m, 2H), 1.47(m, 2H), 2.38(m, 2H), 2.52(m, 2H), 3.00-3.14(m, 6H), 3.25(m, 2H), 3.68(m, 2H), 4.43(m, 1H), 4.62(m, 1H), 5.09(s, 2H), 6.72(s, 1H), 7.04(s, 1H), 7.16(s, 1H), 7.37-7.44(m, 5H), 7.65(s, 1H), 7.72(d, 1H), 7.81(d, 1H), 8.07(d, 1H)	639

Example 30: Synthesis of 1-{1-[1-(N-benzyl-N-methylcarbamoyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(30)

100mg(0.206 mmol) of the compound prepared in Example 6 was dissolved in 1mℓ of tetrahydrofuran, and 27mg(0.23 mmol) of N-benzyl-N-methylamine was added thereto. Then, 0.16mℓ(1.93M in toluene) of phosgene solution was added dropwise thereto at 0℃. The resulting mixture was stirred for 1 hour at room temperature, 1mℓ of water was added thereto, and then this solution was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and subjected to column chromatography (eluent: dichloromethane/methanol=93/7, v/v) to obtain 81mg(0.128 mmol, Yield 62%) of the title compound.

^{1}H-NMR($CDCl_3$) δ 1.20(m, 2H), 1.49(d, 2H), 2.40(br, 2H), 2.56-2.85(m, 8H), 2.93-3.20(m, 5H), 3.29(br, 1H), 3.52(m, 4H), 3.65(d, 2H), 3.73(m, 2H), 4.31(s, 2H), 5.14(s, 2H), 6.71(d, 1H), 7.07(s, 1H), 7.29(m, 10H), 7.73(d, 1H), 7.75 (s, 1H), 7.82(d, 1H), 8.05(d, 1H)

FAB (M+1) 633

Example 31: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroquinolin-1-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(31)

The title compound was obtained according to the same procedure as Example 30 except that 1,2,3,4-tetrahydroquinoline was used instead of N-benzyl-N-methylamine.

Example 32: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(32)

The title compound was obtained according to the same procedure

as Example 30 except that 1,2,3,4-tetrahydroisoquinoline was used instead of N-benzyl-N-methylamine.

Example 33: Synthesis of 1-{1-[1-(4-biphenylmethyl)piperidin-4-yl methyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(33)

100mg(0.206 mmol) of the compound prepared in Example 6 was dissolved in 3mℓ of tetrahydrofuran, 45mg(0.24 mmol) of 4-phenylbenzaldehyde and 52mg(0.24 mmol) of sodium triacetoxyborohydride were added thereto, and the the resulting mixture was stirred for 10 hours at room temperature. 1mℓ of 1N HCl-methanol solution was added to the reaction solution, which was then stirred for 30 minutes, basified and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated and subjected to column chromatography (eluent: dichloromethane/methanol=93/7, v/v) to obtain 100mg(0.154 mmol, Yield 75%) of the title compound.

Example 34: Synthesis of 3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(4-phenoxybenzyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(34)

The title compound was obtained according to the same procedure as Example 33 except that 4-phenoxybenzaldehyde was used instead of 4-phenylbenzaldehyde.

Physico-chemical data of the compounds prepared in Examples 31 to 34 are represented in the following Table 4.

Table 4

COM. NO.	^{1}H-NMR(CDCl$_3$)	FAB MS (M+1)
31	1.12(m, 2H), 1.43(d, 2H), 1.89(m, 2H), 2.39(s, 2H), 2.57(t, 2H), 2.70(m, 3H), 2.90-3.20(br, 7H), 3.30(s, 1H), 3.52(m, 2H), 3.69(d, 2H), 3.75(d, 2H), 5.10(s, 2H), 6.69(d, 1H), 6.84(m, 2H), 7.04(m, 3H), 7.16(s, 1H), 7.31(m, 1H), 7.37(m, 3H), 7.61(s, 1H), 7.74(d, 1H), 7.81(d, 1H), 8.04(d, 1H)	645
32	1.12(m, 2H), 1.43(d, 2H), 1.89(m, 2H), 2.39(s, 2H), 2.75(t, 2H), 2.85-3.15(br, 5H), 3.41(br, 2H), 3.52(br, 4H), 3.69(d, 2H), 3.75(d, 2H), 4.37(s, 2H), 5.11(s, 2H), 6.74(s, 1H), 7.00- 7.70(m, 11H), 7.79(d, 1H), 7.84(d, 1H), 8.06(d, 1H)	645
33	1.31(m, 3H), 1.50(m, 2H), 1.70(m, 4H), 1.91(m, 1H), 2.05(s, 1H), 2.41(s, 2H), 2.75(m, 1H), 2.90(m, 1H), 3.01(br, 2H), 3.09(m, 1H), 3.31(m, 1H), 3.51(s, 2H), 3.71(s, 2H), 5.12(s, 2H), 6.72(s, 1H), 7.10(s, 1H), 7.17(s, 1H), 7.20-7.70(m, 14H), 7.79(d, 1H), 7.84(d, 1H), 8.07(d, 1H)	652
34	1.31(m, 2H), 1.51(m, 2H), 1.90(m, 4H), 1.91(m, 1H), 2.05(s, 1H), 2.42(s, 2H), 2.75(m, 1H), 2.87(m, 2H), 3.01(br, 2H), 3.09(m, 1H), 3.31(m, 1H), 3.51(s, 2H), 3.71(s, 2H), 5.13(s, 2H), 6.72(s, 1H), 6.95-7.70(m, 16H), 7.79(d, 1H), 7.84(d, 1H), 8.07(d, 1H)	668

Example 35: Synthesis of 1-[1-(1-isobutoxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(35)

The title compound was obtained in a yield of 80% according to the same procedure as Example 7 except that isobutylchloroformate was used instead of acetyl chloride.

^{1}H-NMR($CDCl_3$) δ 0.86(d, 6H), 1.04(m, 2H), 1.31(br, 1H), 1.47(m, 2H), 1.86(m, 1H), 2.38(br, 2H), 2.61(m, 3H), 2.99(br, 3H), 3.07(br, 2H), 3.29(br, 1H), 3.42(br, 1H), 3.66(d, 2H), 3.77(d, 2H), 4.08(br, 2H), 5.08(s, 2H), 6.69(s, 1H), 7.03(s, 1H), 7.14(s, 1H), 7.32(m, 1H), 7.37(m, 3H), 7.52(s, 1H), 7.72(d, 1H), 7.80(d, 1H), 8.03(d, 1H)

FAB (M+1) 586

Example 36: Synthesis of 1-{1-[1-(benzyloxycarbonyl)piperidin-4-yl] methyl-1H-imidazol-5-yl}methyl-3-(naphthalen-1-yl)carbonyl-1H-pyrrole (36)

62.6㎎(0.28 mmol) of the compound prepared in Preparation 5-3) was dissolved in 1㎖ of dimethylformamide, and 60㎎(1.5 mmol) of sodium hydride was added thereto. The mixture was stirred for 30 minutes at room temperature, 115㎎(0.30 mmol) of the compound prepared in Preparation 1-4) was added thereto, and then the resulting mixture was stirred for 1 hour. The solvent was removed under reduced pressure and 5㎖ of saturated aqueous sodium bicarbonate solution was added to the residue. This solution was extracted with 20㎖ of ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (eluent: dichloromethane/methanol=95/5, v/v) to obtain 110㎎(0.21 mmol, Yield 75%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.93-1.49(br, 5H), 2.50(s, 2H), 3.58(d, 2H), 4.18(br, 2H), 5.05(s, 2H), 5.12(s, 2H), 6.63(s, 1H), 6.70(s, 1H), 7.09(s, 1H), 7.12 (s, 1H), 7.28-7.60(m, 10H), 7.89(d, 1H), 7.95(d, 1H), 8.10(d, 1H)

FAB : 533 (M+H)

Example 37: Synthesis of 1-[1-(1-acetylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(naphthalen-1-yl)carbonyl-1H-pyrrole(37)

110mg(0.211 mmol) of the compound prepared in Example 36 was dissolved in 10mℓ of methanol, and 20mg of $Pd(OH)_2/C$ was added thereto. Then, the mixture was stirred for 3 hours under hydrogen atmosphere during which benzyloxycarbonyl group was removed. The reactants were filtered through a cellite to remove the catalyst and the solvent was removed under reduced pressure. The unpurified residue was dissolved in 5mℓ of dimethylformamide, and 16.5mℓ(0.232 mmol) of acetyl chloride was added thereto. The reaction solution was stirred for 30 minutes at room temperature and the solvent was removed under reduced pressure. To the residue was added 5mℓ of saturated aqueous sodium bicarbonate solution, which was then extracted with 20mℓ of ethyl acetate. The organic layer was washed with aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was subjected to column chromatography (eluent: dichloromethane/methanol=9/1, v/v) to obtain 20.3mg(0.046 mmol, Yield 22%) of the title compound.

^1H NMR($CDCl_3$) δ 1.11(m, 3H), 1.41(s, 3H), 2.06(s, 3H), 2.27(m, 1H), 2.78(m, 1H), 3.68(m, 2H), 4.58(d, 1H), 5.11(s, 2H), 6.69(s, 1H), 6.70(s, 1H), 7.11(s, 1H), 7.20(s, 1H), 7.50(m, 3H), 7.60(m, 1H), 7.90(m, 2H), 7.98(d, 1H), 8.12(d, 1H)

FAB : 441 (M+1)

Preparation 6: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole

234mg(1 mmol) of the compound prepared in Preparation 2-3) was dissolved in 2mℓ of dimethylformamide, 230mg(1.2 mmol) of EDC and 162mg(1.7 mmol) of HOBT were added thereto, and the resulting mixture was stirred for 5 minutes at 0℃. To this reaction solution was added 88mg(1 mmol) of N-methylpiperazine, which was then stirred for 5 hours at room temperature. The solvent was removed under reduced pressure and 10mℓ of saturated aqueous potassium carbonate solution was added to the residue. The resulting mixture was extracted with ethyl acetate, washed with aqueous sodium chloride solution and water and then concentrated. The concentrate was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=85/15, v/v) to obtain 240mg(0.75 mmol) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.13(br, 2H), 1.88(s, 3H), 1.75-2.08(br, 2H), 2.98(br, 2H), 3.41(br, 2H), 6.85(s, 1H), 7.12(s, 1H), 7.35-7.58(m, 4H), 7.76(d, 1H), 7.82(d, 1H), 8.11(d, 1H), 10.20(br, 1H)

FAB 320 (M+H)

Preparation 7: Synthesis of 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl}carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole

234mg(1 mmol) of the compound prepared in Preparation 2-3) was dissolved in 2mℓ of dimethylformamide. 230mg(1.2 mmol) of EDC, 101mg(1 mmol) of triethylamine and 162mg(1.7 mmol) of HOBT were added thereto and the resulting mixture was stirred for 5 minutes at 0°C. To the reaction solution was added 102mg(1 mmol) of N,N,N'-trimethylethylenediamine, which was then stirred for 5 hours at room temperature. The solvent was removed under reduced pressure and 10 mℓ of saturated aqueous potassium carbonate solution was added to the

residue. The resulting mixture was extracted with ethyl acetate, washed with aqueous sodium chloride solution and water, concentrated, and then subjected to silica gel column chromatography(eluent: dichloromethane/ methanol=85/15, v/v) to obtain 257mg(0.8 mmol) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.89(br, 3H), 2.15(br, 4H), 2.44(br, 2H), 2.75 (br, 1H), 3.0(br, 1H), 3.36(br, 2H), 6.84(s, 1H), 7.07(s, 1H), 7.38-7.43(m, 4H), 7.78(d, 1H), 7.83(d, 1H), 8.1(br, 1H), 10.05(br, 1H)

FAB 322 (M+H)

Example 38: Synthesis of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl) methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(na phthalen-1-yl)-1H-pyrrole(38)

612mg(2.0 mmol) of the compound prepared in Preparation 6 was dissolved in 10mℓ of dimethylformamide, 264mg(6.6 mmol) of sodium hydride(60%) was added thereto at 0°C, and then the resulting mixture was stirred for 5 minutes. 765mg(2.2 mmol) of the compound prepared in Preparation 1-4) was added thereto and the mixture was stirred for 5 hours at room temperature. The solvent was removed by distillation under reduced pressure and 10mℓ of water was added to the residue. The resulting solution was extracted twice with 20mℓ of ethyl acetate, dried over magnesium sulfate, concentrated, and then subjected to silica gel column chromatography(eluent: dichloromethane/methanol=90/10, v/v) to obtain 930mg(Yield 74%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.86(m, 2H), 1.07(m, 2H), 1.24(m, 2H), 1.38(m, 1H), 1.52(m, 2H), 2.65(br, 2H), 3.00-3.50(br, 4H), 3.69(d, 2H), 4.16 (br, 2H), 5.09 (s, 2H), 5.11(s, 2H), 6.73 (d, 1H), 7.12 (s, 1H), 7.21 (s, 1H), 7.25-7.32 (m, 6H), 7.35-7.41 (m, 4H), 7.78(d, 1H), 7.83(d, 1H),

8.01(d, 1H)

FAB (M+H) 631, $C_{38}H_{42}N_6O_3$

Example 39: Synthesis of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl}carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(39)

612mg(2.0 mmol) of the compound prepared in Preparation 7 was dissolved in 10mℓ of dimethylformamide, 264mg(6.6 mmol) of sodium hydride(60%) was added thereto at 0°C, and then the resulting mixture was stirred for 5 minutes. 765mg(2.2 mmol) of the compound prepared in Preparation 1-4) was added thereto and the mixture was stirred for 5 hours at room temperature. The solvent was removed by distillation under reduced pressure and 10mℓ of water was added to the residue. This solution was extracted twice with 20mℓ of ethyl acetate, dried over magnesium sulfate, concentrated and then subjected to silica gel column chromatography(eluent: dichloromethane/methanol=90/10, v/v) to obtain 870mg(Yield 69%) of the title compound.

^1H NMR($CDCl_3$ +CD_3OD) δ 1.00(m, 2H), 1.31-1.40(m, 3H), 2.54- 2.70(m, 9H), 3.50-3.80(m, 6H), 4.01(br, 2H), 4.50(s, 1H), 4.96(s, 2H), 5.07(s, 2H), 6.65(s, 1H), 7.01(s, 1H), 7.03(s, 1H), 7.13(s, 1H), 7.18-7.30(m, 7H), 7.45(s, 1H), 7.52(s, 1H), 7.64(d, 1H), 7.72(d, 1H), 7.80(d, 1H)

FAB (M+H) 633: $C_{38}H_{44}N_6O_3$

Example 40: Synthesis of 1-[1-(1-methoxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(40)

40-1) 3-(4-Methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-[(piperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-1H-pyrrole

227mg(0.36 mmol) of the compound prepared in Example 38 was dissolved in 5mℓ of methanol, 2g of potassium hydroxide was added thereto, and the resulting mixture was reacted for 8 hours under reflux. The reaction solution was cooled down, extracted twice with 10mℓ of ethyl acetate, dried over anhydrous sodium sulfate and then evaporated under reduced pressure to obtain the title compound in a yield of 80%.

^{1}H NMR($CDCl_3$) δ 1.15(br, 2H), 1.48(d, 2H), 1.75-1.98(m, 6H), 2.45(t, 2H), 2.91(br, 1H), 3.02(d, 2H), 3.31(br, 1H), 3.50-3.85(m, 7H), 5.10(s, 2H), 6.70(s, 1H), 7.09(m, 1H), 7.13(s, 1H), 7.30(t, 1H), 7.35-7.50 (m, 4H), 7.74(d, 1H), 7.80(d, 1H), 8.01(d, 1H)

FAB (M+H): 497, $C_{30}H_{36}N_6O$

40-2) 1-[1-(1-Methoxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole

30mg(62 μmol) of the compound prepared in Example 40-1) was added to 2mℓ of dichloromethane, and 5.4mg(6.9 μmol) of methylchloroformate was added thereto using a syringe. This mixture was reacted for 2 hours, the solvent was removed under reduced pressure, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=85/15, v/v) to obtain 27.8mg(50 μmol, Yield 80%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.06(m, 4H), 1.40(m, 1H), 1.51(d, 2H), 1.93(s, 3H), 2.02(br, 1H), 2.60(br, 3H), 2.98-3.60(br, 4H), 3.64(s, 3H), 3.69(d, 2H), 4.10(br, 2H), 5.14(s, 2H), 6.73(d, 1H), 7.12(s, 1H), 7.18(s, 1H), 7.30(t, 1H), 7.35-7.55(m, 4H), 7.77(d, 1H), 7.82(d, 1H), 8.02(d, 1H)

FAB (M+H):555, $C_{32}H_{38}N_6O_3$

Example 41: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-1-[1-(1-methylsulfonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-4-(naphthalen-1-yl)-1H-pyrrole(41)

30㎎(62 μmol) of the compound prepared in Example 40-1) was added to 2㎖ of dichloromethane, and 7.8㎎(6.9 μmol) of methanesulfonyl chloride was added thereto using a syringe. This mixture was reacted for 2 hours, the solvent was removed under reduced pressure, and then the residue was subjected to silica gel column chromatography (eluent: dichloromethane/methanol=90/10, v/v) to obtain 25㎎(4.5 μmol, Yield 87%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.03(m, 4H), 1.43(m, 1H), 1.52(d, 2H), 1.98(s, 3H), 2.03(br, 1H), 2.62(br, 3H), 2.04-3.65(br, 4H), 3.64(s, 3H), 3.69(d, 2H), 4.10(br, 2H), 5.13(s, 2H), 6.72(d, 1H), 7.11(s, 1H), 7.19(s, 1H), 7.31(t, 1H), 7.32-7.53(m, 4H), 7.78(d, 1H), 7.83(d, 1H), 8.01(d, 1H)

FAB (M+H): 575, $C_{32}H_{38}N_6O_3$

Example 42: Synthesis of 1-[1-(1-acetylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(42)

30㎎(62 μmol) of the compound prepared in Example 40-1) was added to 2㎖ of dichloromethane, and 5.4㎎(6.9 μmol) of acetyl chloride was added thereto using a syringe. This mixture was reacted for 2 hours, the solvent was removed under reduced pressure, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=80/20, v/v) to obtain 26㎎(4.8 μmol, Yield 78%) of the title compound.

^1H NMR($CDCl_3$) δ 1.00-1.12(m, 2H), 1.32-1.45(m, 2H), 1.52-1.58 (m, 2H), 1.90-2.10(m, 8H), 2.35(m, 1H), 2.93(t, 1H), 3.07(m, 1H), 3.10-3.70(br, 4H), 3.69(d, 1H), 7.75(d, 1H), 4.57(d, 1H), 5.12(s, 2H), 6.74(d, 1H), 7.12(d, 1H), 7.20(s, 1H), 7.34(d, 1H), 7.39-7.47(m, 4H), 7.78(d, 1H), 7.85(d, 1H), 8.01(d, 1H)

FAB (M+H): 539, $C_{32}H_{38}N_6O_2$

Example 43: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(2-phenylethylcarbonyl)-piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(43)

62mg(125 μmol) of the compound prepared in Example 40-1) was dissolved in 2mℓ of dichloromethane, and 22mg(128 μmol) of 3-phenylpropionyl chloride was added thereto. This mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 49mg(Yield 62%) of the title compound.

^1H NMR($CDCl_3$) δ 0.77(m, 1H), 0.90-1.20(m, 2H), 1.35(m, 1H), 1.43(d, 1H), 1.51(d, 1H), 1.91(s, 3H), 1.80-2.00(br, 2H), 2.34(t, 1H), 2.55(m, 3H), 2.75(t, 1H), 2.85(br, 5H), 3.63(m, 3H), 3.72(d, 1H), 4.60(d, 1H), 5.11(s, 2H), 6.71(d, 1H), 7.09(d, 1H), 7.14-7.35(m, 7H), 7.38(m, 4H), 7.75(d, 1H), 7.81(d, 1H), 8.01(d, 1H)

FAB (M+H): 629, $C_{39}H_{44}N_6O_2$

Example 44: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-[1-(1-phenoxyacetylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-1H-pyrrole(44)

62mg(125 μmol) of the compound prepared in Example 40-1) was dissolved in 2mℓ of dichloromethane, and 23mg(128 μmol) of phenoxyacetyl chloride was added thereto. This mixture was reacted for 3 hours, the solvent was removed, and then the residue was subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 50mg(Yield 63%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.90-1.12(m, 4H), 1.28(m, 1H), 1.46(d, 2H), 1.70-2.00(br, 1H), 1.84(s, 3H), 2.38(t, 1H), 2.86(t, 1H), 2.80-3.50(br, 5H), 3.59(m, 2H), 3.89(d, 1H), 4.48(d, 1H), 4.58(q, 2H), 5.05(s, 2H), 6.69(d, 1H), 6.86(d, 2H), 6.91(t, 1H), 7.04(d, 1H), 7.13(d, 1H), 7.20-7.30(m, 3H), 7.30-7.60(m, 4H), 7.71(d, 1H), 7.77(d, 1H), 7.98(d, 1H)

FAB (M+H): 631, $C_{38}H_{42}N_6O_3$

Example 45: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylmethyloxy)carbonylpiperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(45)

1.19g(7.52 mmol) of (naphthalen-2-yl)methanol was dissolved in 15mℓ of toluene, and 1.04g(7.53 mmol) of potassium dicarbonate was added thereto. To this solution was added 3.89mℓ(1.93M in toluene) of phosgene solution at 0℃, and the whole solution was stirred for 2 hours at room temperature. The reactants were filtered to remove solid materials and then 0.108g(0.222 mmol) of the compound prepared in Example 40-1) and 0.046mℓ(0.33 mmol) of triethylamine were added thereto. The resulting mixture was stirred for 1 hour at room temperature, and distilled under reduced pressure to remove the solvent. 10mℓ of saturated aqueous sodium bicarbonate solution was added to the residue, which was then extracted with ethyl acetate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was

subjected to silica gel column chromatography(eluent: dichloromethane/ methanol=95/5, v/v) to obtain 65mg(0.097 mmol, Yield 43%) of the title compound.

^{1}H NMR($CDCl_3$) δ 0.94(m, 3H), 1.45(br, 3H), 2.61(m, 3H), 2.96 (s, 3H), 3.15(m, 2H), 3.75(m, 4H), 4.06(d, 2H), 4.71(br, 2H), 5.06(s, 2H), 5.18(s, 1H), 6.77(s, 1H), 7.15-8.00(m, 17H)

FAB(M+H): 681, $C_{42}H_{44}O_3N_6$

Examples 46 to 48

The compounds represented in the following Table 5 were obtained according to the same procedure as Example 45.

Table 5-1

COM. NO.	NMR($CDCl_3$)	FAB (M+1)
46	0.89(d, 6H), 1.07(m, 2H), 1.37(m, 1H), 1.47-1.50(m, 5H), 1.65(m, 1H), 1.80-2.10(br, 4H), 2.59(br, 2H), 3.01-3.60(br, 5H), 3.90- 4.20(m, 5H), 5.11(s, 2H), 6.73(d, 1H), 7.12(d, 1H), 7.18(s, 1H), 7.31(t, 1H), 7.31-7.54(m, 4H), 7.77(d, 1H), 7.79(d, 1H), 8.01(d, 1H), $C_{36}H_{46}N_6O_3$	611
47	1.00-1.12(m, 3H), 1.38(m, 1H), 1.51(d, 3H), 1.95(s, 3H), 2.63(br, 3H), 3.00-3.60(br, 4H), 3.68(d, 2H), 4.12(br, 3H), 5.05(s, 2H), 5.11(s, 2H), 6.72(d, 1H), 7.00-7.07(m, 2H), 7.12(s, 1H), 7.20(s, 1H), 7.25-7.35(m, 3H), 7.36-7.52(m, 4H), 7.78(d, 1H), 7.83(d, 1H), 8.03(d, 1H), $C_{38}H_{41}FN_6O_3$	649

Table 5-2

COM. NO.	NMR($CDCl_3$)	FAB (M+1)
48	1.08(br, 2H), 1.20(d, 1H), 1.45-1.60(m, 4H), 3.25(br, 2H), 3.72(m, 2H), 4.01-4.21(br, 4H), 4.71(d, 1H), 5.15(s, 1H), 6.26-6.29(m, 1H), 6.60(d, 1H), 6.76(d, 1H), 7.14-7.45(m, 8H), 7.45-6.62(m, 3H), 7.63(s, 1H), 7.82(d, 1H), 7.83(d, 1H), 7.98(d, 1H), $C_{40}H_{44}N_6O_3$	657

Example 49: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(49)

100㎎(0.206 mmol) of the compound prepared in Example 40-1) and 39㎎(0.22 mmol) of 2-naphthoic acid were dissolved in 1㎖ of dimethylformamide. 59㎎(0.31 mmol) of EDC and 42㎎(0.31 mmol) of HOBT were added thereto, and the resulting mixture was stirred for 2 hours at room temperature. The solvent was removed by distillation under reduced pressure, then the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, concentrated and subjected to silica gel column chromatography(eluent: dichloromethane/methanol=95/5, v/v) to obtain 88㎎(0.14 mmol, Yield 68%) of the title compound.

^{1}H NMR($CDCl_3$) δ 1.05(br, 3H), 1.38(m, 1H), 1.56(d, 2H), 1.70-1.90(br, 6H), 2.36(br, 1H), 2.47(t, 1H), 2.82-3.07(br, 3H), 3.32(br, 2H), 3.63(t, 2H), 4.07(br, 1H), 4.67(d, 1H), 5.09(s, 2H), 6.73(d, 1H), 6.84(d, 1H), 7.08(d, 1H), 7.31(d, 1H), 7.25-7.55(m, 10H), 7.58 (d, 1H), 7.73(d,

1H), 7.80(d, 1H), 8.02(d, 1H)

FAB (M+1): 627, $C_{39}H_{42}N_6O_2$

Examples 50 to 51

The compounds represented in the following Table 6 were obtained according to the same procedure as Example 49 except that trans-cinnamic acid and 2-(2-propyl)thiazole-4-carboxylic acid, respectively, were used instead of 2-naphthoic acid.

Table 6

COM. NO.	NMR ($CDCl_3$)	FAB (M+1)
50	1.08(br, 3H), 1.33-1.45(m, 1H), 1.58(d, 2H), 1.75-1.95(br, 2H), 1.83(s, 3H), 2.36(br, 1H), 2.47(br, 1H), 2.85-3.10(br, 3H), 3.15-3.50(br, 2H), 3,62-3.80(m, 2H), 4.02-4.15(br, 1H), 4.62-4.78(br, 1H), 5.10(s, 2H), 6.74(d, 1H), 6.82(d, 1H), 7.09(d, 1H), 7.18(s, 1H), 7.30-7.55(m, 10H), 7.60(d, 1H), 7.76(d, 1H), 7.80(d, 1H), 8.03(d, 1H), $C_{41}H_{42}N_6O_2$	627
51	1.01(br, 1H), 1.24(m, 2H), 1.37(d, 7H), 1.40-1.65(m, 3H), 1.70-2.02(m, 7H), 2.59(br, 1H), 2.92(br, 2H), 3.28(br, 2H), 3.71(d, 2H), 4.49(br, 1H), 4.65(br, 1H), 5.13(s, 2H), 6.73(d, 1H), 7.09(d, 1H), 7.18(s, 1H), 7.32(d, 1H), 7.35-7.50(m, 4H), 7.68(s, 1H), 7.70(d, 1H), 7.84(d, 1H), 8.03(d, 1H), $C_{37}H_{43}N_7O_2S$	650

Example 52: Synthesis of 1-{1-[1-(N-benzyl-N-methylcarbamoyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(52)

100mg(0.206 mmol) of the compound prepared in Example 40-1) was dissolved in 1mℓ of tetrahydrofuran and 27mg(0.23 mmol) of N-benzyl-N-methylamine was added thereto at 0℃. 0.16mℓ(1.93M in toluene) of phosgene solution was added dropwise thereto, and the resulting solution was stirred for 1 hour at room temperature. 1mℓ of water was added to the solution, which was then extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated and subjected to silica gel column chromatography(eluent: dichloromethane/ methanol=93/7, v/v) to obtain 86mg(0.133 mmol, Yield 64%) of the title compound.

^{1}H NMR($CDCl_3$+CF_3COOH) δ 1.24(m, 3H), 1.52(m, 4H), 2.44(s, 3H), 2.65-3.00(m, 8H), 3.04(s, 2H), 3.63(d, 2H), 4.00(br, 1H), 4.17(d, 2H), 4.32(s, 2H), 5.52(s, 2H), 7.21-7.63(m, 12H), 7.94(d, 1H), 7.96(d, 1H), 8.01(d, 1H), 9.06(s, 1H)

FAB (M+1): 644, $C_{39}H_{45}N_7O_2$

Example 53: Synthesis of 1-{1-[1-(N,N-dimethylcarbamoyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(53)

The title compound represented in Table 7 was obtained according to the same procedure as Example 52 except that N,N-dimethylamine was used instead of N-benzyl-N-methylamine.

Example 54: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroquinolin-1-ylcarbonyl)piperidin-4-yl] methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(54)

The title compound represented in Table 7 was obtained according

to the same procedure as Example 52 except that 1,2,3,4-tetrahydroquinoline was used instead of N-benzyl-N-methylamine.

Example 55: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(55)

The title compound represented in Table 7 was obtained according to the same procedure as Example 52 except that 1,2,3,4-tetrahydroisoquinoline was used instead of N-benzyl-N-methylamine.

Table 7

COM. NO.	NMR($CDCl_3$)	FAB MS (M+1)
53	1.00-1.30(m, 3H), 1.31-1.67(m, 3H), 1.70-2.05(m, 6H), 2.59(m, 2H), 2.74(s, 6H), 2.89(m, 2H), 3.20-3.50(m, 2H), 3.68(m, 4H), 5.10(s, 2H), 6.74(d, 1H), 7.12(d, 1H), 7.20(s, 1H), 7.34(d, 1H), 7.39-7.47(m,4H), 7.78(d, 1H), 7.85(d, 1H), 8.01(d, 1H), $C_{33}H_{41}N_7O_2$	568
54	1.03-1.30(m, 4H), 2.31-2.51(m, 3H), 1.70-2.20(m, 10H), 2.57(t, 2H), 2.72(t, 1H), 2.90(br, 2H), 3.31(br, 2H), 3.54(t, 1H), 3.66(m, 2H), 3.81(d, 1H), 5.11(s, 2H), 6.68(d, 1H), 6.83(t, 1H), 6.92(d, 1H), 7.1(m, 2H), 7.12(d, 1H), 7.18(s, 1H), 7.31(d, 1H), 7.44(m, 4H), 7.76(d, 1H), 7.82(d, 1H), 8.02(d, 1H) ; $C_{40}H_{45}N_7O_2$	656
55	0.9-2.1(m, 12H), 2.72(t, 2H), 2.80-3.95(m, 12H), 4.37(s, 2H), 5.12(s, 2H), 6.72(s, 1H), 7.00-7.70(m, 11H), 7.78(d, 1H), 7.82(d, 1H), 8.05(d, 1H) ; $C_{40}H_{45}N_7O_2$	656

Example 56: Synthesis of 1-{1-[1-(4-biphenylmethyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(56)

100mg(0.206 mmol) of the compound prepared in Example 40-1) was dissolved in 3mℓ of tetrahydrofuran, 45mg(0.24 mmol) of 4-phenylbenzaldehyde and 52mg(0.24 mmol) of sodium triacetoxyborohydride were added thereto, and the resulting solution was stirred for 10 hour at room temperature. 1mℓ of 1N HCl-methanol solution was added to the reaction solution, which was then stirred for 30 minutes, basified and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, concentrated and subjected to silica gel column chromatography(eluent: dichloromethane/methanol=93/7, v/v) to obtain 100mg(0.151 mmol, Yield 75%) of the title compound.

FAB MS(M+1): 663

Example 57: Synthesis of 3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(4-phenoxybenzyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(57)

The title compound was obtained according to the same procedure as Example 56 except that 4-phenoxybenzaldehyde was used instead of 4-phenylbenzaldehyde.

FAB MS(M+1): 679

Experimental Example 1

Analysis of in vitro inhibitory activity for Ras farnesyl transferase

In the present experiment, Ras farnesyl transferase produced by genetic recombination techniques according to the improved Pompliano's method (Pompliano et al., Biochemistry, 1992, 31, 3800) was used, and Ras substrate(Ras-CVLS) protein described in Korean Patent Appln. No. 97-14409 was used after it has been purified according to the known method(see, Chung et al., Biochimica et Biophysica Acta, 1992, 278, 1129).

The enzyme reaction was performed in 50$\mu\ell$ of 50mM Sodium HEPES buffer solution containing 25mM of potassium chloride, 25mM of magnesium chloride, 10mM of DTT and 50μM of zinc chloride. 1.5 μM of Ras substrate protein, 0.15μM of tritium-farnesylpyrophosphate and 4.5nM of farnesyl transferase were used.

More specifically, in the initial step, farnesyl transferase was added to the above buffer solution, reaction was maintained for 30 minutes at 37℃ and then the reaction was stopped by adding 1$m\ell$ of ethanol solution containing 1M HCl. The formed precipitates were adsorbed to GF/B filter using Hopper harvestor(Hopper #FH 225V) for filter-binding, washed with ethanol, and then radioactivity of the dried filter was measured using LKB β counter. Enzyme titer was measured in the unsaturated state of substrate where the concentrations of Ras substrate protein and farnesyl transferase have quantitative relationship. The compound according to the present invention dissolved in dimethyl sulfoxide(DMSO) was added to the reaction solution in an amount of less than 5% of the total reaction solution, and then the enzyme inhibitory activity thereof was measured. The enzyme inhibitory activity was represented by percentage of the amount of farnesyl incorporated into the Ras substrate protein in the presence of the test compound to that in the absence of the test compound. IC_{50} of the test compound

was defined as the concentration at which 50% of the enzyme activity was inhibited.

To evaluate the selective enzyme inhibitory activity of the compound according to the present invention, inhibitory activity on geranylgeranyl transferase was measured. Geranylgeranyl transferase was purified from bovine brain according to the method modified from Schaber's method(Schaber et al., J. Biol. Chem. 1990, 265, 14701), and substantially the same experimental procedure as that for farnesyl transferase was performed on geranylgeranyl pyrophosphate and Ras-CVIL substrate protein.

The test results are represented in the following Table 8.

Experimental Example 2

Analysis of in vivo inhibitory activity for Ras farnesyl transferase

In the present experiment, Rat2 cell line which expresses C-Harvey-Ras protein having transforming activity and Rat2 cell line(Korean patent application No. 97-14409) which is transformed with fused protein of H-Ras substituted with polybasic lysine domain at C-terminus of K-Ras were used. The experiment was performed by the modified Declue's method(Declue. J. E. et al., Cancer Research, 1991, 51, 712). Hereinafter, the experimental method will be described in more detail.

3×10^5 cells of transformed Rat2 fibroblast cell line were sprayed on 60mm cell cultivation dish and cultivated for 48 hours in a cell incubator at 37℃ and after 50% or more of density was reached, it was treated with the test compounds. The compound according to the

present invention dissolved in dimethylsulfoxide(DMSO) was used. 1% concentration of dimethylsulfoxide was used in both control and test groups. After 4 hours from the treatment with the compound, methionine labeled with 150 μCi of radioactive isotope [^{35}S] per 1mℓ of medium was added and after cultivating for 20 hours, the cells were washed with physiological saline water. The cells were lysed using 1mℓ of cold cell lysis buffer solution(50mM of Sodium HEPES buffer solution containing 5mM of magnesium chloride, 1mM of DTT, 1% NP 40, 1mM of EDTA, 1mM of PMSF, 2 μM of leupeptin, 2 μM of pepstatin A and 2 μM of antipain) and the supernatant wherein the cells were lysed was obtained by high-velocity centrifugation of 12,000g $\times$ 5 minutes. The amount of radioisotope in the supernatent was measured and standardized to obtain a quantitative result in immunoprecipitation reaction and then, Y13-259, a monoclonal antiboby specifically binding to Ras protein(Furth, M. E. et al., J. Virol, 1982, 43, 294) was added and reacted for 15 hours at 4℃. Protein A(combined with goat anti-murine imunoglobulin antibody)-agarose suspension was added to the solution and reacted for 1 hour at 4℃ and then, to remove the unspecific binding product, immunoprecipitates were washed with a buffer solution (50mM Tris chloride buffer solution containing 50mM of sodium chloride, 0.5% of sodium dioxycholate, 0.5% of NP 40 and 0.1% of SDS). The precipitates were added to a buffer solution for electrophoresis and boiled and then, electrophoresis was performed using 13.5% of SDS polyacrylamide gel. Atfer electrophoresis, the gel was fixed and dried. Then, the gel was exposed to X-ray film, developed and printed. From the result of the experiment, intensities of band of protein combined with or without farnesyl of Ras protein were measured, and the concentration of the test compound inhibiting 50% of farnesyl binding was defined as CIC_{50}, an in vivo Ras farnesyl transferase inhibitory activity. The test results are shown in the following Table 8.

Table 8-1

COM. NO.	H-Ras $IC_{50}(\mu M)$	H-Ras $CIC_{50}(\mu M)$	K-Ras $IC_{50}(\mu M)$	K-Ras $CIC_{50}(\mu M)$
1	0.0085	0.1	2.4	1-10
2	0.009	0.1	6	10-100
3	0.001	0.01-0.1	0.016	10-50
4	0.0036	0.01-0.1	0.026	10-50
5	0.0025	0.01-0.1	0.01-0.1	1-10
6	0.008	0.01-0.1	0.01-1	1-10
7	0.0018	0.01-0.1	0.01-0.1	10-100
8	0.0012	0.01-0.1	0.01-0.1	10-50
9	0.001-0.01	0.01-0.1	0.01-1	1-50
10	0.001-0.01	0.01-0.1	0.01-1	1-50
11	0.001-0.01	0.01-0.1	0.01-1	1-50
12	0.001-0.01	0.01-0.1	0.01-1	1-50
13	0.001-0.01	0.01-0.1	0.01-1	1-50
14	0.0021	0.01-0.1	0.01-1	1-50
15	0.001	0.01-0.1	0.01-1	1-50
16	0.001-0.01	0.01-0.1	0.01-1	10-100
17	0.001-0.01	0.01-0.1	0.01-1	10-100
18	0.001	0.01-0.1	0.01-1	1-50
19	0.007	0.01	0.02	1-10
20	0.006	0.01	0.01	1-10
21	0.01-0.1	0.01-0.1	0.05	1-10
22	0.009	0.01-0.1	0.02	1-10
23	0.008	0.01-0.1	0.02	1-10
24	0.006	0.01-0.1	0.015	1-10

Table 8-2

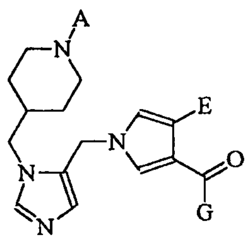
COM. NO.	H-Ras $IC_{50}(\mu M)$	H-Ras $CIC_{50}(\mu M)$	K-Ras $IC_{50}(\mu M)$	K-Ras $CIC_{50}(\mu M)$
25	0.006	0.01-0.1	0.027	1-10
26	0.004	0.01-0.1	0.01-0.1	10-50
27	0.009	0.01-0.1	0.015	1-10
28	0.012	0.01-0.1	0.008	1-10
29	0.0025	0.01-0.1	0.01-0.1	10-50
30	0.0025	0.01-0.1	0.006	1-10
31	0.004	0.01-0.1	0.02	10-50
32	0.002	0.01-0.1	0.012	1-10
33	0.005	0.01-0.1	0.01-0.1	1-10
34	0.011	0.01-0.1	0.01-0.1	1-10
35	0.006	0.01-0.1	0.01-0.1	1-10
36	0.2	10	> 100	50
37	0.35	1-10	10-100	10-50
38	0.0038	0.0125	0.015	2.5
39	0.3	1	1.5	30-100
40	0.0016	0.03	0.0042	10-50
41	0.003	0.05	0.01	10-50
42	0.0012	0.025	0.006	10-50
43	0.002	0.05	0.01	10-50
44	0.002	0.05	0.011	10-50
45	0.0018	0.035	0.012	10
46	0.0022	0.025	0.016	10-50
47	0.0033	0.0125	0.0065	4
48	0.0033	0.0125	0.007	1

Table 8-3

COM. NO.	H-Ras $IC_{50}(\mu M)$	H-Ras $CIC_{50}(\mu M)$	K-Ras $IC_{50}(\mu M)$	K-Ras $CIC_{50}(\mu M)$
49	0.0018	0.35	0.012	10
50	0.0017	0.03	0.008	10-50
51	0.003	0.005	0.01	10-50
52	0.0023	0.05	0.01	10-50
53	0.003	0.05	0.0085	10-50
54	0.011	0.025	0.04	10-50
55	0.002	0.025	0.04	10-50
56	0.005	0.05	0.02	5
57	0.011	0.025	0.01	10

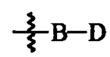
WHAT IS CLAIMED IS:

1. A piperidine derivative represented by the following formula (1):



(1)

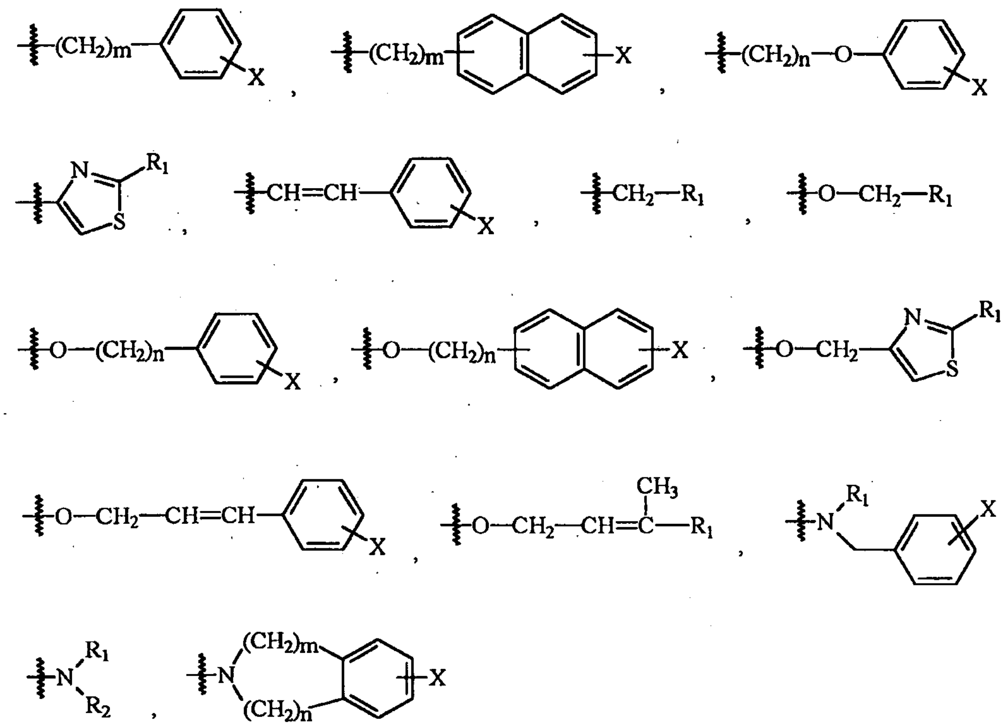
in which

A represents hydrogen, lower alkyl, or  ,

wherein

B represents CH_2, C=O or SO_2, and

D represents a radical selected from the following group:



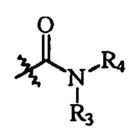
In the definition for the substituent D,

m denotes an integer of 0 to 3,

n denotes an integer of 1 to 3,

X represents hydrogen, phenyl, phenoxy, lower alkyl, lower alkoxy, halogen, nitro, or amino which is optionally substituted by benzyl or lower alkyl,

R_1 and R_2 independently of one another represent hydrogen, lower alkyl, C_3-C_6-cycloalkyl, lower alkyl substituted by C_3-C_6-cycloalkyl, aryl or heteroaryl,

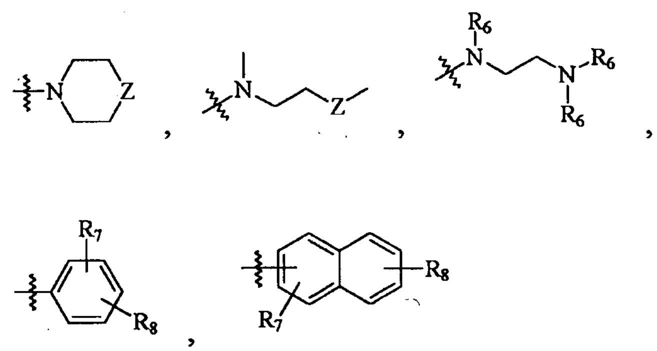
E represents hydrogen, phenyl, naphthyl or  ,

wherein

R_3 and R_4 independently of one another represent hydrogen, lower alkyl,

aryl or $-(CH_2)_{n'}-Y-R_5$ (wherein Y represents O or S, n' denotes an integer of 2 to 4, and R_5 represents lower alkyl),

G represents a radical selected from the following group:



wherein

Z represents O, S, SO_2 or N-R_6 (wherein R_6 represents hydrogen or lower alkyl),

R_7 and R_8 independently of one another represent hydrogen, lower alkyl, lower alkoxy, halogen, cyano, hydroxycarbonyl, aminocarbonyl, aminothiocarbonyl, hydroxy, phenyl or phenoxy, or a pharmaceutically acceptable salt thereof.

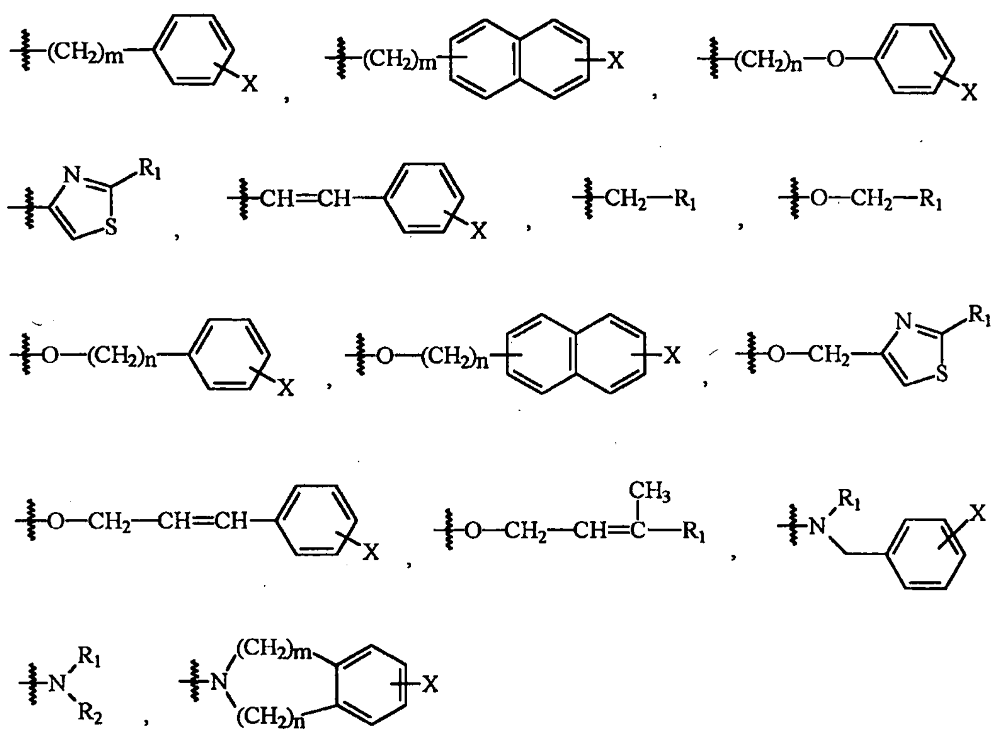
2. The compound of claim 1 wherein

A represents hydrogen, lower alkyl, or $-B-D$,

wherein

B represents CH_2, C=O or SO_2,

D represents a radical selected from the following group:



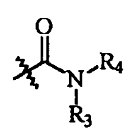
In the definition for the substituent D,

m denotes an integer of 0 to 1,

n denotes an integer of 1 to 2,

X represents hydrogen,

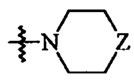
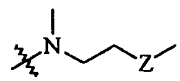
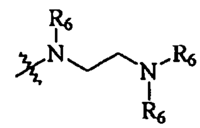
R_1 and R_2 independently of one another represent hydrogen or lower alkyl,

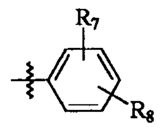
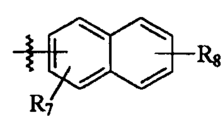
E represents hydrogen, phenyl, naphthyl, or  ,

wherein

R_3 and R_4 independently of one another represent hydrogen, lower alkyl, or 2-methoxyethyl,

G represents a radical selected from the following group:

 ,  ,  ,

 , 

wherein

Z represents O or N-R_6 (wherein R_6 represents methyl),

R_7 and R_8 independently of one another represent hydrogen.

3. The compound of claim 1 which is selected from a group consisting of:

1-[1-(1-benzyloxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(1);

3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1-[1-(piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(2);

1-[1-(1-acetylpiperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(3);

1-[1-(1-methylsulfonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-(morpholin-4-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(4);

1-[1-(1-benzyloxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(5);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(6);

1-[1-(1-acetyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(7);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-1-[1-(1-methylsulfonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-4-(naphthalen-1-yl)-1H-pyrrole(8);

1-{1-[1-(N-benzylcarbamoyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(9);

1-{1-[1-(N-butylcarbamoyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(10);

1-{1-[1-(N-cyclohexylcarbamoyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(11);

1-[1-(1-heptanoyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(12);

1-{1-[1-(4-methoxybenzylcarbonyl)-piperidin-4-ylmethyl]-1H-imidazol-5-yl methyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(13);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(1-phenoxyacetyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(14);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(2-phenylethylcarbonyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(15);

1-{1-[1-(4-biphenylacetyl)-piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(16);

1-[1-(1-methoxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(17);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-[1-(1-propionyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-1H-pyrrole(18);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-1-ylmethyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(19);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylmethyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl

}-1H-pyrrole(20),

1-{1-[1-(3,7-dimethylocta-2,6-dien-1-yloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(21),

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-1-{1-[1-(3-methyl-2-buten-1-yl oxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-4-(naphthalen-1-yl)-1H-pyrrole(22),

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-1-{1-[1-(3-methylbutan-1-yloxy carbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-4-(naphthalen-1-yl)-1H-pyrrole(23),

1-{1-[1-(4-fluorobenzyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-yl methyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(24),

1-{1-[1-(cinnamyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl} -3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole (25),

1-{1-[1-(2-isopropylthiazol-4-ylmethyloxycarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(26),

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole(27);

1-[1-(1-cinnamoylpiperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(28),

1-{1-[1-(2-isopropylthiazol-4-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H -pyrrole(29),

1-{1-[1-(N-benzyl-N-methylcarbamoyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H -pyrrole(30);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroquinolin-1-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-yl methyl}-1H-pyrrole(31);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl)piperidin-4-ylmethyl]-1H-imidazol-5-yl methyl}-1H-pyrrole(32);

1-{1-[1-(4-biphenylmethyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(33);

3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1-{1-[1-(4-phenoxybenzyl)piperidin-4-ylmethyl]-1H-imidazol-5-ylmethyl}-1H-pyrrole (34);

1-[1-(1-isobutoxycarbonyl-piperidin-4-ylmethyl)-1H-imidazol-5-ylmethyl]-3-[N-(2-methoxyethyl)-N-methyl]carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(35);

1-{1-[1-(benzyloxycarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(naphthalen-1-yl)carbonyl-1H-pyrrole (36);

1-[1-(1-acetylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(naphthalen-1-yl)carbonyl-1H-pyrrole(37);

1-[1-(1-benzyloxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(38);

1-[1-(1-benzyloxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl}carbamoyl-4-(naphthalen-1-yl)-1H-pyrrole(39);

1-[1-(1-methoxycarbonylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(40);

3-(4-methylpiperazin-1-yl)carbonyl-1-[1-(1-methylsulfonylpiperidin-4-yl) methyl-1H-imidazol-5-yl]methyl-4-(naphthalen-1-yl)-1H-pyrrole(41);

1-[1-(1-acetylpiperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-3-(4-methyl-piperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(42);

3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(2-phenylethyl carbonyl)-piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(43);

3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-[1-(1-phenoxyacetyl piperidin-4-yl)methyl-1H-imidazol-5-yl]methyl-1H-pyrrole(44);

3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylmethyloxy)carbonylpiperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(45);

1-{1-[1-(3-methylbutyloxy)carbonylpiperidin-4-yl]methyl-1H-imidazol-5-yl} methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole (46);

1-{1-[1-(4-fluorobenzyloxy)carbonylpiperidin-4-yl]methyl-1H-imidazol-5-yl} methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole (47),

1-{1-[1-(cinnamyloxycarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl -3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(48),

3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(naphthalen-2-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(49);

1-{1-[1-(cinnamoyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(50);

1-{1-[1-(2-isopropylthiazol-4-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole (51);

1-{1-[1-(N-benzyl-N-methylcarbamoyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole (52);

1-{1-[1-(N,N-dimethylcarbamoyl)piperidin-4-yl]methyl-1H-imidazol-5-yl} methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(53) ;

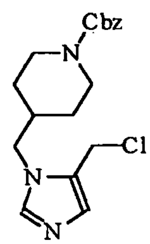
3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetra-hydroquinolin-1-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(54);

3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(1,2,3,4-tetra-

hydroisoquinolin-2-ylcarbonyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(55);
1-{1-[1-(4-biphenylmethyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1H-pyrrole(56); and
3-(4-methylpiperazin-1-yl)carbonyl-4-(naphthalen-1-yl)-1-{1-[1-(4-phenoxy benzyl)piperidin-4-yl]methyl-1H-imidazol-5-yl}methyl-1H-pyrrole(57).

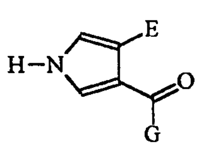
4. A process for preparing a piperidine derivative of formula (1) as defined in claim 1 characterized in that

(a) a compound represented by the following formula (2a):



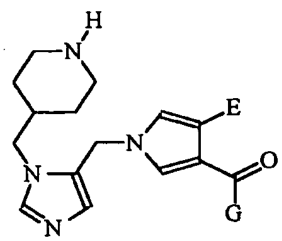
(2a)

wherein Cbz represents benzyloxycarbonyl, is reacted in a solvent in the presence of a base with a compound represented by the following formula (3):



(3)

wherein E and G are defined as claim 1, then the protecting group Cbz is eliminated to produce a compound represented by the following formula (1a):



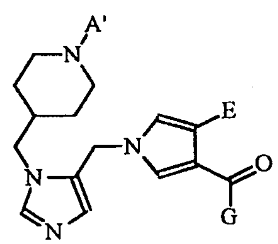
(1a)

wherein E and G are defined as claim 1;

(b) the compound of formula (1a) is reacted in a solvent with a compound represented by the following formula (4):

A'—W (4)

wherein A' is the same with A defined in claim 1 except that A' is not hydrogen, and W represents hydrogen, hydroxy or reactive leaving group, to produce a compound represented by the following formula (1b):



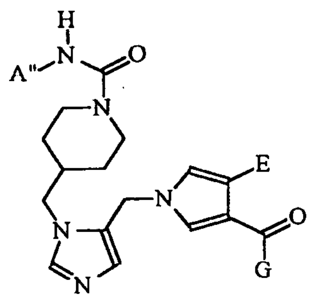
(1b)

wherein A' is defined as previously described and E and G are defined as claim 1;

(c) the compound of formula (1a) is reacted in a solvent with a compound represented by the following formula (5):

A"—N=C=O (5)

wherein A" represents lower alkyl, benzyl or C_3-C_6-cycloalkyl, to produce a compound represented by the following formula (1c):



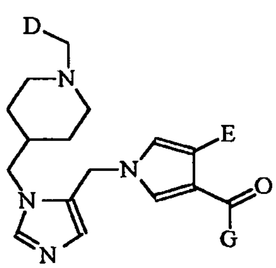
(1c)

wherein A" is defined as previously described and E and G are defined as claim 1;

(d) the compound of formula (1a) is reacted in a solvent in the presence of a reducing agent with a compound represented by the following formula (6):

D–CHO (6)

wherein D is defined as claim 1, to produce a compound represented by the following formula (1d):



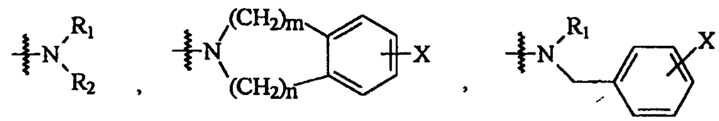
(1d)

wherein D, E and G are defined as claim 1; or

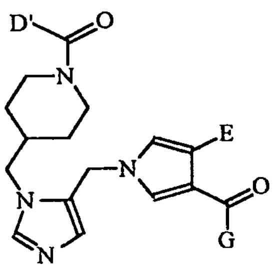
(e) the compound of formula (1a) is reacted in a solvent with phosgene and a compound represented by the following formula (7):

D'H (7)

wherein D' represents a radical selected from the following group:



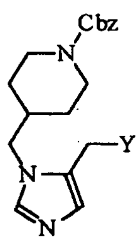
wherein m, n, X, R_1 and R_2 are defined as claim 1, to produce a compound represented by the following formula (1e):



(1e)

wherein D' is defined as previously described and E and G are defined as claim 1.

5. A compound represented by the following formula (2):

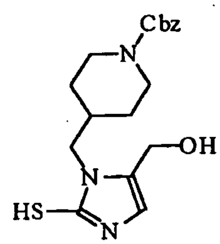


(2)

wherein Y represents hydroxy or chloro.

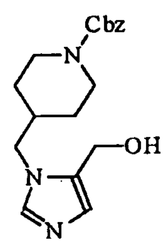
6. A process for preparing the compound of formula (2) as defined in claim 5 characterized in that

(f) a compound represented by the following formula (8):



(8)

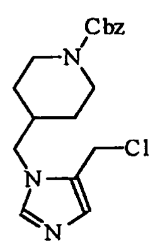
is desulfurated in an organic solvent in the presence of nitric acid to produce a compound represented by the following formula (2b):



(2b)

; or

(g) the compound of formula (2b) is reacted with thionyl chloride($SOCl_2$) to produce a compound represented by the following formula (2a):



(2a)

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7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound of formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of claim 7 useful for treating or preventing cancer.

9. The pharmaceutical composition of claim 7 useful for treating or preventing restenosis.

10. The pharmaceutical composition of claim 7 useful for treating or preventing atherosclerosis.

11. The pharmaceutical composition of claim 7 useful for treating or preventing infections from hepatitis delta and related viruses.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00051

A. CLASSIFICATION OF SUBJECT MATTER

IPC^6: C 07 D 401/14, 401/06, 413/14; A 61 K 31/445, 31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC^6: C 07 D 401/00, 413/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/36 587 A1 (MARCH & CO) 09 October 1997 (09.10.97), claims 1-12.	1,7-11
A	WO 97/36 900 A1 (MARCH & CO) 09 October 1997 (09.10.97), claims 1-14.	1-4,7-11
A	WO 97/36 892 A1 (MARCH & CO) 09 October 1997 (09.10.97), claims 1-21.	1-4,7-11
A	WO 97/36 890 A1 (MARCH & CO) 09 October 1997 (09.10.97), claims 1-27.	1-4,7-11
A	WO 97/38 665 A2 (MARCH & CO) 23 October 1997 (23.10.97), claims 8-38.	1-4,7-11
A	WO 93 /19 059 A1 (PFIZER LIMITED) 30 September 1993 (30.09.93), preparations 30,42.	5,6

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A“ document defining the general state of the art which is not considered to be of particular relevance
„E“ earlier application or patent but published on or after the international filing date
„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O“ document referring to an oral disclosure, use, exhibition or other means
„P“ document published prior to the international filing date but later than the priority date claimed
„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
06 April 1999 (06.04.99)	30 April 1999 (30.04.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Hammer Telephone No. 1/53424/374

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00051

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 428 434 A2 (SANOFI S.A.) 22 May 1991 (22.05.91), compound 120 (47 678A).	5
A	WO 95/00 507 A1 (THE BOOTS COMP.) 05 January 1995 (05.01.95), page 18, line 3.	1,5

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 99/00051

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9736587	09-10-97	AU A1 27221/97	22-10-97
		CA AA 2250232	09-10-97
		EP A1 906099	07-04-99
		GB AO 9613599	28-08-96
WO A1 9736900	09-10-97	AU A1 25988/97	22-10-97
		EP A1 891360	20-01-99
		GB AO 9609666	10-07-96
WO A1 9736892	09-10-97	AU A1 25932/97	22-10-97
		EP A1 891353	20-01-99
		GB AO 9616736	25-09-96
WO A1 9736890	09-10-97	AU A1 24303/97	22-10-97
		EP A1 891351	20-01-99
		AU A1 24301/97	22-10-97
		AU A1 24325/97	22-10-97
		AU A1 24326/97	22-10-97
		AU A1 26020/97	22-10-97
		AU A1 26021/97	22-10-97
		AU A1 26057/97	22-10-97
		AU A1 26058/97	22-10-97
		AU A1 26702/97	22-10-97
		AU A1 27307/97	22-10-97
		CA AA 2249615	09-10-97
		EP A1 891333	20-01-99
		EP A1 891334	20-01-99
		EP A1 891339	20-01-99
		EP A1 891343	20-01-99
		EP A1 891355	20-01-99
		EP A1 891356	20-01-99
		EP A1 891357	20-01-99
		EP A1 891361	20-01-99
		EP A1 904076	31-03-99
		WO A1 9736585	09-10-97
		WO A1 9736875	09-10-97
		WO A1 9736876	09-10-97
		WO A1 9736881	09-10-97
		WO A1 9736886	09-10-97
		WO A1 9736896	09-10-97
		WO A1 9736897	09-10-97
		WO A1 9736898	09-10-97
		WO A1 9736901	09-10-97
		GB AO 9617255	25-09-96
		GB AO 9613462	28-08-96
		GB AO 9617277	25-09-96
		GB AO 9617257	25-09-96
		GB AO 9617254	25-09-96
		GB AO 9617282	25-09-96
		GB AO 9617258	25-09-96
		GB AO 9617280	25-09-96
		GB AO 9617278	25-09-96
		GB AO 9617279	25-09-96
WO A2 9738665	23-10-97	AU A1 27347/97	07-11-97
		CA AA 2249601	23-10-97
		WO A3 9738665	27-11-97
		GB AO 9609981	17-07-96
WO A1 9319059	30-09-93	AU A1 37483/93	21-10-93
		BR A 9306138	23-06-98
		CZ A3 9402295	12-04-95
		EP A1 632808	11-01-95
		FI A 944428	23-09-94
		FI AO 944428	23-09-94
		GB AO 9301638	17-03-93
		HU AO 9402744	28-12-94
		JP T2 7501556	16-02-95
		NO AO 943540	23-09-94
		NO A 943540	21-11-94
		SK A3 1140/94	12-04-95
		AP AO 9300500	30-04-93
		CN A 1077716	27-10-93
		GB AO 9206462	06-05-92
		HR A1 930283	31-08-97
		IL AO 105099	08-07-93
		MX A1 9301694	01-09-93
		ZA A 9302079	26-09-94